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SYMPOSIUM ON THE TREATMENT OF PNEUMONIA

The following clinics are included in this Symposium

Leon H. Collins, Jr. SPECIFIC THERAPY, OXYGEN THERAPY AND SYMPTOMATIC
TREATMENT OF PNEUMONIA

Henry U. Hopkins NURSING CARE AND DIET IN PNEUMONIA.

Simon S. Leopold ARTIFICIAL PNEUMOTHORAX IN THE TREATMENT OF LOBAR
PNEUMONIA.

I. S. Ravdin SOME SURGICAL COMPLICATIONS OF PNEUMONIA.

CLINIC OF DR LEON H COLLINS, JR

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SPECIFIC THERAPY, OXYGEN THERAPY AND SYMPTOMATIC TREATMENT OF PNEUMONIA

Specific Therapy—Of the various types of therapy which might be termed specific for pneumonia, it would appear that the one meeting with the widest acceptance at the present time is the use of specific antipneumococcus serum prepared according to the method of Felton. In this country the vast majority of the nonepidemic forms of pneumonia are produced by pneumococci. In adults, pneumococci, Types I and II, account for approximately two thirds of the cases of pneumonia. The highly virulent Type III pneumococcus infection, for which to date no satisfactory antiserum is available, is still much less frequently encountered than either Types I or II.

Although the use of specific pneumococcus antiserum seems to be increasing, nevertheless, until recently, the principal deterrents to its wider use have been the time and rather prolonged laboratory procedure involved in the older methods of pneumococcus typing for diagnostic purposes. Fortunately, these former difficulties have now been largely overcome by the perfection of a method utilizing the Neufeld reaction for the immediate typing of pneumococci directly from the sputum.¹

This method of typing is being carried on in most of the larger hospitals at the present time. If the patient is being treated at his home a sputum specimen is collected in a sterile Petri dish. This is taken to the hospital laboratory where,

within a few minutes, if pneumococci are present in the sputum, it should be possible to diagnose the type with a very high degree of accuracy. This improved method of pneumococcus typing is based upon the fact that when pneumococci are brought in contact with a homologous type of rabbit pneumococcus antiserum there occurs very rapidly a swelling, "Quellung," in the capsule of the pneumococcus. The studies of Sabin¹ would suggest that this reaction is highly type specific.

The materials necessary for carrying out the Neufeld reaction, according to the Sabin technic, consist of a microscope, slides, cover glasses, alkaline methylene blue for staining, and small tubes containing the various types of rabbit pneumococcus antiserum for typing purposes.

In addition to this increased speed in pneumococcus typing there recently have occurred decided advances in the attempts to subdivide the pneumococci which have in the past been conveniently classed as "Pneumococcus Group IV." Miss Cooper² and her colleagues have succeeded in splitting this group into 29 different types of pneumococci. Pneumococcus rabbit antisera are now commercially available for the identification of pneumococci I to XIX and it is probable that in the near future others will be added to the present list.

From the standpoint of the pneumococcus antiserum itself there have been recent improvements. These have consisted chiefly in a further reduction in the substances which presumably are the cause of serum reactions and in a greater concentration of the pneumococcus antibodies. Thus, with the newer pneumococcus antisera, a given dosage can be given in smaller bulk and with less probability of serum reaction than was possible in the past.

For therapeutic purposes at the present time antisera are commercially available against pneumococcus Types I, II, and VII. It is possible that the future will provide sera against other higher types of pneumococci.

As soon as a satisfactory typing has been obtained, if antiserum is to be administered, it should be begun as soon as

possible. There is increasing evidence to suggest that the most satisfactory results from antiserum administration are obtained when treatment is started early in the disease. Because the common method of preparing pneumococcus antisera is the immunization of horses to increasing doses of pneumococci, it is apparent that evidence in the patient's previous clinical history suggesting serum sensitivity or sensitivity to horse proteins should be carefully sought.

At the present time sensitivity to the antiserum to be injected is tested for by the injection of 1 or 2 drops into the conjunctiva or into the dermis. In the former position, if the patient is sensitive, conjunctival hyperemia and edema with lacrimation manifest themselves within a few minutes. In the latter position local hyperemia, edema, and itching indicate that the patient is serum sensitive and that serum injection should not proceed until the patient has been desensitized.

When one is assured that serum sensitivity is not present, the serum is then injected. Specific pneumococcus antiserum should ordinarily be administered intravenously. Because of the immediate reaction that may occur during or very shortly after the injection of antiserum, one should always have immediately available a syringe containing 1 cc of 1:1000 adrenalin solution. It is usually wise to limit the initial dose to 10,000 units, although this caution is probably not necessary. Subsequent doses may be 10,000 or 20,000 units given at four hour intervals. Even though it be necessary to awaken the patient, this schedule should be maintained. The evidence of satisfactory serum effect is a decline in the temperature curve. The serum administration should be continued until the temperature has returned to almost normal levels, or until, for some special reasons, its further use seems unwise. As a rule, for the proper treatment of a case with specific pneumococcus antiserum, from 100,000 to 200,000 units of serum are necessary. In patients with persisting pneumococemia or with spreading consolidations, more than 200,000 units may be necessary.

Serum sickness, usually occurring about ten days following the administration of the antiserum, may still be encountered. Adrenalin (0.2 to 0.5 cc) hypodermically will usually relieve the symptoms. It is believed by some that adequate catharsis and calcium lactate (0.5 Gm four times daily) are of distinct value in preventing this phenomenon. It is always wise to warn the patient and his family some days previously about the time that serum sickness may possibly be expected.

Other forms of treatment that might be considered in the category of specific therapy for pneumonia are vaccine therapy, quinine administration, Huntoon's antibody solution, and the administration to children of serum from individuals recently convalesced from pneumonia of the same pneumococcus type.

In England, a vaccine containing pneumococci, streptococci and bacillus influenzae appears to be used quite frequently. Such treatment, however, to date in this country has not met with very wide usage.

For many years quinine and its derivatives, particularly optochin (ethyl hydrocupreine), have been considered by some observers to be, both clinically and experimentally, a "specific" against pneumococci. Some of the European reports on its use, especially those from Germany, have been rather optimistic. The clinical results in this country, however, of quinine administration in pneumonia do not appear outstanding at the present.

Huntoon's antibody solution has been used quite extensively in this country. In the earlier years in some instances severe reactions followed its injection. It is claimed that with the more recent product, these chill-producing substances have been removed.

For several years evidence has been accumulating which appears to suggest that in the blood of healthy adults there are antibodies which may be transferred by injection to children ill with pneumonia. Such a method affords a possible means of nonspecific antibody administration where the type of pneumococcus present prevents the use of specific pneumo-

coccus antiserum^{3,4} The 2 following cases shown in Figs 1, 2 are illustrative of this form of therapy

Case I.—E. C., seen with Dr John McK Mitchell. A previously healthy girl, aged six had developed symptoms and signs suggesting a beginning pneumonia of the right lower lobe. Temperature was 101.4 F. Leukocytes were 16,500 of which 55 per cent were polymorphonuclear neutrophils and

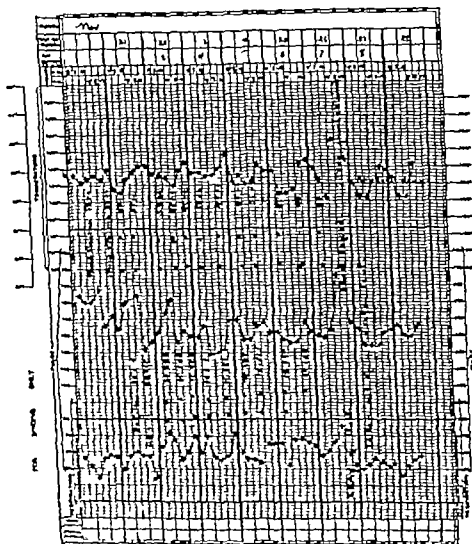


Fig 1—Specific and non specific serum therapy in pneumococcus (Type I) pneumonia

35 per cent lymphocytes. 33 per cent of the polymorphonuclears were young forms. A laryngeal swab cultured on blood agar showed a few pneumococci. A blood agar culture of the sputum showed a few pneumococci, some *Bacilli influenzae*, and a few hemolytic streptococci. The clinical diagnosis was a probable pneumococcus pneumonia of the right lower lobe. Pneumococcus anti serum (Felton) Types I and II was given at first intramuscularly and later intravenously. Plasma collected from healthy adults was given at the same time at first intramuscularly and later intravenously. The doses of serum and plasma are shown in Fig 1. A chest roentgenogram taken on the seventh day

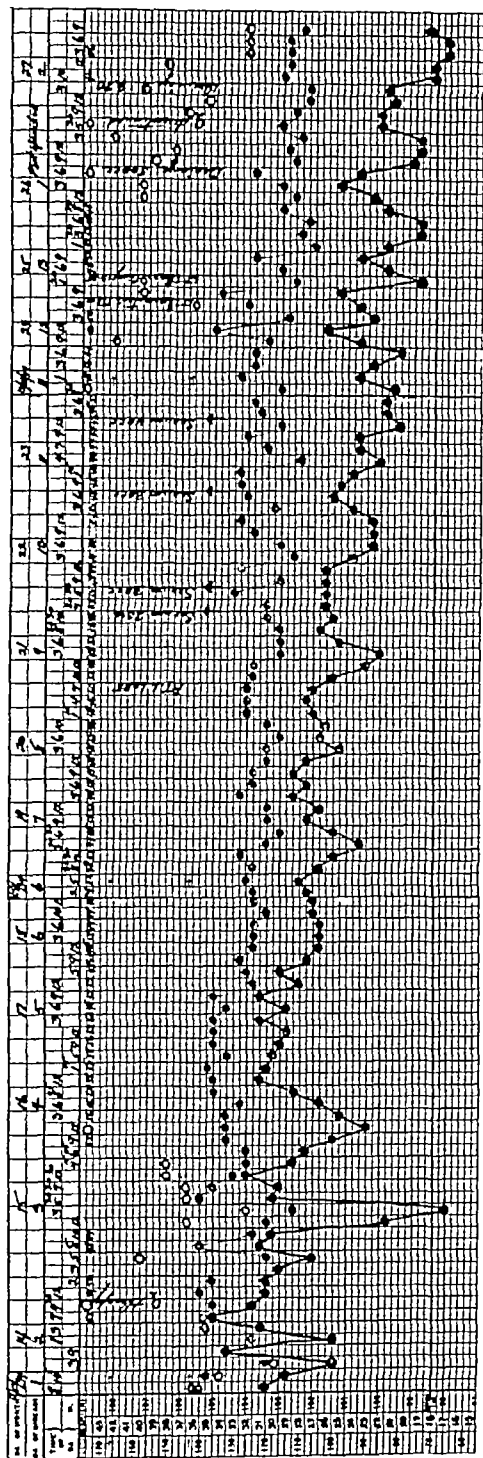


Fig 2 —Nonspecific serum therapy in pneumonia

of the disease showed obscuration of the entire chest with considerable displacement of the heart to the left, typical of a massive empyema or a collection of fluid. The right pleural sac was drained surgically. The fluid obtained showed a pure culture of pneumococcus Type I. After surgical drainage the child made a slow but eventually perfect recovery. In addition to the serum therapy this patient was in an oxygen tent from the first to the eighth day of the disease.

Case II.—B. S., seen with Dr. Thomas Fitz Hugh Jr. A girl, aged eight, after having a cold for a week developed symptoms and signs suggesting a lobar consolidation of the left upper and left lower lobes. Sputum culture showed pneumococcus Group IV. Because of the cyanosis and dyspnea the child was placed in an oxygen tent from the second to the fourteenth day of the disease. On the eighth day of the disease a spread occurred, involving the entire right lower lobe. From the ninth to the eleventh day serum collected from healthy adults was administered. The amounts given were 20, 30, 30 and 40 cc. respectively. On the thirteenth day a thoracotomy was done on the left side. Thereafter she made a rapid and perfect recovery.

Oxygen Therapy—The accumulated facts seem to indicate that in the majority of patients with pneumonia, at some time during the course of the disease, the oxygen concentration in the arterial blood may fall below normal levels. This fall (arterial anoxemia) is roughly parallel in its severity to the intensity of the cyanosis as observed in the lips or the finger nail beds.

At the present time one cannot describe with certainty the specific disturbances in pneumonia which account for this arterial anoxemia. Rapid shallow breathing, the circulation of blood through poorly aerated portions of lung tissue, and degenerative changes in the alveolar cells themselves, all probably contribute to its production.

In such a complicated disease as pneumonia it would be extremely hazardous to designate those symptoms that are directly and solely traceable to the anoxemia. The analysis of symptoms in individuals observed at high altitudes or those observed at sea level while breathing air containing reduced tensions of oxygen, suggests that dyspnea, cyanosis, changes in cardiac rate, and mental symptoms may reasonably be ascribed to oxygen lack *per se*. Easy fatigability has long been observed when individuals are breathing low tensions of oxygen.

As far as pneumonia is concerned, it has been observed that with the proper administration of oxygen dyspnea and cyanosis are lessened or completely relieved. Reductions in pulse and respiratory rates may be seen, and frequently delirium is diminished or disappears altogether. In Table 1 are given the results of oxygen administration in pneumonia in one of our series⁵ of patients observed at the Hospital of the University of Pennsylvania.

From the standpoint of treatment, the degree of anoxemia in pneumonia affords an index of the severity of the infection in much the same manner that pneumococcemia suggests, other things being equal, a poorer prognosis in an individual case. In cases where the arterial oxygen saturation is found to have fallen below 70 per cent recovery is rare.

The principal indications for the administration of oxygen in pneumonia are dyspnea, cyanosis, rising pulse and respiratory rates, and delirium. For the optimum results to be obtained, the administration should be started at the first appearance of dyspnea and cyanosis, and continued until these features are absent when the patient is allowed to breathe ordinary room air.

Great advances have been made in the technic of oxygen administration in pneumonia since Dr. George E. Holtzapple⁶ recorded, in 1887, his experience with the use of oxygen generated at the bedside of a patient with pneumonia. His paper apparently is the first dealing with this subject in the records of the Surgeon General's Office.

At the present time oxygen may be administered by nasal catheter, oxygen tent, or an oxygen chamber. Because of the expense of installation, oxygen chambers are still rather few in this country. For general purposes I prefer the oxygen tent. Many good tents are now on the market and in most hospitals and communities they are daily in operation. In my opinion, in addition to satisfactory gas control, the crucial test of a given tent is the degree of comfort that it is able to afford to the patient. If the patient objects to the tent in any respect, the technic of the administration of the oxygen is

TABLE 1
DETECTABLE EFFECTS OF OXYGEN ADMINISTRATION

Case No.	Cyanosis.		Temperature.		Pulse		Respiration.	
	Before.	After	Before.	After	Before	After	Before.	After
1	++	0	*	*	*	*	*	*
2	++	+ or 0	*	*	*	*	*	*
3	++	++	*	*	*	*	*	*
4	++	+	*	*	*	*	*	*
5	+++	0	102 ²	102 ²	120	120	36	32
6	+++	+++	*	*	*	*	*	*
7	++	+ or 0	102	100	144	104	32	28
	First 2 hours							
8	+++	+	*	*	*	*	*	*
9	++	or 0	*	*	*	*	*	*
10	++	0	104 ⁴	102 ²	120	86	28	24
11	++	+	101 ⁴	98	120	80	*	*
12	+	+	*	*	*	*	*	*
13	+++	+++	*	*	*	*	*	*
	First 24 hours							
14	++	+	101	101	112	120	28	24
15	++	+	*	*	*	*	*	*
16	++	0	*	*	*	*	*	*
17	(Negro)		101 ²	99	136	102	40	32
18	+++	+++	*	*	*	*	*	*
19	++	0	103 ²	100 ⁴	128	112	40	32
20	++	+	101 ⁴	100	102	90	36	30
21	++	0	103 ²	102	120	100	56	56
22	(Negro)		*	*	*	*	*	*
23	++	+	*	*	*	*	*	*
24	++	+ or 0	101 ²	103 ²	96	108	36	26
25	++	+	*	*	*	*	*	*
26	++	0	*	*	*	*	*	*
27	++	or 0	*	*	*	*	*	*
28	++	0	*	*	*	*	*	*
29	++	0	*	*	*	*	*	*
30	++	0	*	*	*	*	*	*
31	++	0	102 ²	98 ⁴	100	96	32	28
32	(Negro)		*	*	*	*	*	*
33	++	+	*	*	*	*	*	*
34	++	0	*	*	*	*	*	*
35	++	+	*	*	*	*	*	*
36	++	++	*	*	*	*	*	*
37	++	+	*	*	*	*	*	*
38	+++	0	104	99 ⁴	96	88	36	32
39	++	+	*	*	*	*	*	*
40	++	0	100 ⁴	101	116	116	48	36
41	++	++	*	*	*	*	*	*
42	++	+	*	*	*	*	*	*
43	(Negro)		99 ²	99	120	114	32	28
44	++	0	102	100 ²	*	*	40	20
45	+++	0	101 ²	103 ²	144	106	44	28

faulty at some point. If, before starting the administration of oxygen, the purpose of the treatment is made clear to the

patient, much unnecessary apprehension and disturbance will be avoided

The optimum concentration of oxygen in the air circulating in the tent is about 50 per cent. Higher concentrations may be used for short periods, but it should be remembered that concentrations of 70 per cent maintained for several days in animal experiments apparently produce a widespread injury to lung tissue. In the majority of the later tents an oxygen flow of 6-8 liters per minute will maintain an oxygen concentration of 50 per cent. As tents become older cracks in the fabric are apt to occur, thus allowing oxygen to escape from the tent. One can only be certain of the oxygen concentration of the circulating air by withdrawing samples for analysis. This analysis is easily done with simple portable apparatus that is now widely available. I prefer tents in which, by soda lime absorption, the carbon dioxide in the circulating air may be removed completely. Occasionally it may be desired to allow the expired carbon dioxide to accumulate to some degree in the tent by not allowing the circulating air to pass over the soda lime. Higher carbon dioxide concentrations are easily obtained by using tanks containing both oxygen and carbon dioxide.

Efficient oxygen administration interferes in no way with the use, simultaneously, of any other forms of treatment. In the two patients whose charts have been shown (Figs 1, 2) other forms of treatment were being utilized throughout the course of the oxygen administration.

Finally, it should be remembered that although oxygen differs from a gas such as hydrogen in being nonexplosive, nevertheless, the presence of an atmosphere containing an increased concentration of oxygen may cause materials such as bedding and linen to burn with amazing rapidity. Therefore, signs warning of this danger should be clearly in evidence to prevent open flames or sparks being brought close to the tent. Several accidents have already occurred from the injudicious use of candles and alcohol lamps.

Symptomatic Treatment—In every case of pneumonia

probably the therapeutic consideration of greatest importance is the conservation in every conceivable manner of the patient's strength. It is, therefore, paramount that pain and mental anxiety should be reduced to the minimum. Chest pain resulting from pleurisy is usually relieved by strapping. One of the earliest observed effects of artificial pneumothorax was the reduction or abolition of pleural pain. Codeine sulphate ($\frac{1}{4}$ grain—0.015 Gm) repeated every three or four hours seems to be the most effective drug for a harassing dry cough. It is important, however, that sufficient codeine not be given to abolish the cough reflex. The virtues of morphine sulphate in pneumonia are obvious. Nevertheless, it should be remembered that in some cases, particularly lobular pneumonias associated with relatively high grades of pulmonary edema and cyanosis, repeated doses of morphine may bring about sufficient respiratory depression to cause grave decreases in the oxygen content of the arterial blood. The simultaneous administration of atropine is generally believed to lessen this respiratory depression.

The chest should be examined sufficiently often to determine the presence of a spread of the lesion, evidence of fluid collections in the pleural sac, the apparent functional state of the heart muscle, and the presence of fluid within the pericardial sac. At such times the patient should never be allowed to turn or rise himself with his own effort.

The abdomen should be palpated frequently to detect the earliest trace of distention. It has been suggested by some that abdominal distention is less when the fluids consumed are cool rather than ice cold. A liquid diet, plus enemas daily or on alternate days, may prevent distention throughout the entire disease. Too great care cannot be exercised to assure that the patient does not strain while the enema is being given. At the first appearance of abdominal distention a rectal tube should be left *in situ* and a large turpentine stupe or a flaxseed poultice reaching from ensiform to pubis, and from flank to flank, should be applied immediately. In addition, physostigmine sulphate in doses of $\frac{1}{60}$ grain (0.001 Gm) hypo-

dermically, or pituitrin, 5 to 8 minims (0.3 to 0.5 cc), may be helpful

At times control of delirium is particularly difficult. If the patient has been accustomed to taking alcohol it is probably wise to administer it in generous doses. To avoid morphine's respiratory depressing effect, chloral hydrate (15 grains—1 Gm) or paraldehyde (30 minims—2 Gm) may be administered orally or rectally. For the control of the most severe forms of delirium, Bullowa⁷ has suggested the rectal administration of tribromethanol (avertin) 60 mg per kilo supplemented, if necessary, by the intravenous injection of diallylmalonyl urea (0.005 Gm) per kilo.

In the absence of cardiac decompensation or auricular fibrillation, it is difficult at the present time to justify^{8, 9} the routine digitalization of patients with pneumonia. It is probable that digitals in moderate doses (1½ grains—0.09 Gm), three times daily, will do no harm and possibly may afford better myocardial tone in patients with preexisting cardiovascular disease. Should auricular fibrillation occur, I believe that the patient should be digitalized. Toxic doses, however, always should be carefully avoided.

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CLINIC OF DR HENRY U HOPKINS

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NURSING CARE AND DIET IN PNEUMONIA

THE importance of proper nursing care in pneumonia can not be overestimated. Despite recent advances in therapy, the resistance of the host is still the most important factor in determining the outcome of the disease. Any measure which increases the physical or mental comfort of the patient deserves consideration.

Absolute rest is essential for the patient with pneumonia. Energy conserved by avoiding unnecessary movements may be just that amount required to save an otherwise fatal case. A comfortable position is important. The Fowler or semi-Fowler position is usually selected, but occasionally a patient prefers to lie flat or on his side. In the home, a back rest can be improvised from a chair padded with pillows. One or two pillows will provide support for the knees, and small pillows should be placed under the shoulders and elbows. The patient should not be allowed to sit up to use a bed pan or urinal. Preferably he should not sit up for examination of the back, when this seems essential, he should be raised gently and supported during the examination. A change of position at intervals is desirable, it rests and relaxes the muscles. Visitors should be few, and their stay must be brief. Sedatives may be necessary to insure adequate rest. Barbitol or its derivatives, chloral hydrate, paraldehyde, and codeine are useful. Morphine decreases ventilation, may increase abdominal distention, and occasionally seems to cause mental confusion or delirium, it should be used sparingly.

The room should be well ventilated but without draughts. A cool or cold room is usually most comfortable to the patient, but individual preferences should be respected. The advantages of the open-air treatment in winter weather have not been proved.

A flannel gown (or pajamas) is desirable, this must be changed as soon as it becomes moistened by perspiration. A shoulder blanket should be worn at all times. Blankets may replace sheets, all bedclothes should be of wool to insure warmth without excessive weight. The bed must be kept clean, warm, and dry, moisture favors the development of pressure areas or sores. Local heat to the lower extremities is often soothing. Occasionally a tight flannel jacket or binder helps to relieve pleuritic pain, but usually it merely increases dyspnea. An ice-bag applied to the chest may afford comfort, it should not be used for more than two hours at a time.

A tepid bath should be given once a day, frequent sponges are undesirable. The back requires extra care. It should be rubbed with alcohol, a bathing solution, or cold cream, powder is then applied. All bathing must be done in a warm room.

Cleanliness of the mouth is of extreme importance. In the majority of cases, pneumonia follows infection of the upper respiratory tract. Mouth breathing is very common, frequently it is due to nasal occlusion. The dry, dirty oral cavity furnishes an additional site of potential danger. Recent careful studies have substantiated the belief that proper attention to the mouth and nose lessens the danger of reinfection or superinfection. Moreover, the sense of taste is improved, this makes it easier to maintain an adequate intake of fluids and food. The entire oral cavity should be scrubbed every two hours with an alkaline mouth wash. This is followed by the application of albolene to the tongue and cold cream to the lips. A nasal spray should be used frequently, ephedrine in oil or a simple cleansing solution is satisfactory.

The bowels require careful attention. In the early stages, a laxative may be ordered. An enema is given daily. Abdominal distention of a variable degree is a part of the disease.

picture, it is harmful in proportion to the degree to which it limits respiration. It should be combated by the use of a rectal tube, enemas, stupes or poultices to the abdomen, and the administration of pitressin or pituitrin (1 cc subcutaneously every twenty minutes for two or three doses).

As the disease is of relatively brief duration, the maintenance of an adequate caloric intake is not of major importance, but a high fluid intake (3000 to 5000 cc. per day) is desirable. An adult should be given 50 to 60 Gm. of protein per day, and at least 2000 calories. The preferences of the individual should be considered in preparing the diet, but sufficient variety, the feeding of small amounts each time, and frequent sips of fluid will markedly increase the intake. The patient must be fed by the nurse until he is definitely convalescent.

Milk usually constitutes an important part of the diet, although some clinicians insist that it increases abdominal distention. Hippocrates was apparently the first to express this opinion. The evidence at present seems inconclusive. A quart a day is sufficient, buttermilk may provide an agreeable change. The milk can be given plain or flavored, it may be used in preparing cream soups, custards, or ice cream. Small amounts of water should be offered frequently. Some persons find physiologic salt solution more palatable, and there have been studies which suggest that a high salt intake may be of value during the febrile stage. Fruit juices are usually acceptable—orange juice, grapefruit juice, pineapple juice, grape juice, or lemonade. Lactose or glucose can be added to these to increase the caloric value without rendering them too sweet. Ginger ale and other soft drinks are usually well tolerated. Tomato juice, broths, or thin soups containing strained vegetables are easily prepared. Coffee should not be taken to excess but in moderation it may prove to be valuable. In the unexpectedly severe depression which may follow the use of a sedative, or in sudden collapse, strong coffee by bowel supplees fluid, heat, and a pharmacologic antidote and stimulant. Eggs can be added to the milk or fruit juices, or they may be served alone. Strained cooked cereals, such as oatmeal or

farina, can be used. Alcohol in moderation is useful in selected cases. Small amounts of solid foods may provide a welcome and well-tolerated change from the monotony of an exclusively liquid diet.

Whenever possible, a trained nurse should be in attendance. She should be thoroughly familiar with the disease, and be able to recognize promptly any changes in the condition of the patient. She must learn the personal likes and dislikes of the patient, and she must inspire the confidence of the family. She must arrange for relief, for the patient must never be left alone, delirium may suddenly appear. Accurate and complete bedside notes are essential. A record of the intake and output must be kept. The amount and character of the sputum should be noted. The nurse must dispose of the sputum, preferably by burning it, and supervise the care of dishes and bedding. Familiarity with the methods of oxygen administration is desirable, and she should understand the complications which may follow serum therapy.

Convalescence is often the most trying period, but tact and firmness will usually succeed in keeping the patient quiet until recovery seems definitely assured.

CLINIC OF DR SIMON S LEOPOLD

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ARTIFICIAL PNEUMOTHORAX IN THE TREATMENT OF LOBAR PNEUMONIA

THE use of artificial pneumothorax in the treatment of lobar pneumonia began quite accidentally when Rood,¹ then of the Medical Corps of the U S Army, was doing lung punctures for bacteriologic purposes during the influenzal pneumonia epidemic of 1918. The spontaneous pneumothoraces which sometimes ensued prompted several patients to request further similar treatments and, as the result of this, artificial pneumothorax was instituted deliberately in three patients who were considered moribund. Two recovered.

Foreign clinicians started to use this treatment in 1921 and their results were reviewed last year when the first experimental paper appeared on this subject.² Suffice it to say that up to 1933 artificial pneumothorax had been employed abroad in 50 cases of lobar pneumonia. Nineteen of the subjects were infants and young children, treated for the most part for postpneumonic complications and all recovered. Thirty-one were adults treated on the second to the tenth day and, of these, twenty-eight recovered and three died.

Stimulated by these almost unbelievable results but unwilling to proceed on unsupported evidence, we submitted the problem to experimental study in dogs. Our results were so encouraging that it seemed proper to apply this method to the treatment of lobar pneumonia in man.

In this country, during the past year, 197 cases of lobar pneumonia have been treated by artificial pneumothorax. In

an effort to establish the present status of this treatment, a critical analysis of all of the available data, based on these reported cases, was presented to the American College of Physicians at their last Annual Meeting³

This group of 197 cases comprised 180 adults and 17 children. There were 58 deaths, a mortality of 29.4 per cent.

In view of the fact that the general hospital mortality of lobar pneumonia ranges from 25 to 35 per cent, it was stated that artificial pneumothorax appeared to be neither helpful nor harmful and had no influence on the death rate of this disease. We further expressed the belief that this procedure would have no effect on the mortality of this disease if artificial pneumothorax continued to be used as indiscriminately in the future as it has been in the past.

In an effort to establish the indications for and contraindications to this form of treatment, the cases were analyzed with particular reference to those factors which influence most profoundly the prognosis of lobar pneumonia. These are age, time of treatment in relation to the onset of the disease, bacteriemia, spread, and postpneumonic complications.

In regard to age, it was stated that compression therapy should not be used in childhood because, under conservative treatment, lobar pneumonia at this time of life is a comparatively innocuous disease and also because there is more likelihood in children, so treated, of spontaneous pneumothorax and empyema.

Specific serum therapy is only effective when used early. This is equally true of artificial pneumothorax. Blake⁴ treated 25 cases within the first three days with one death, 18 were treated on the fourth and fifth days with 10 deaths.

In regard to bacteriemia, it appeared that compression therapy had no effect on preexisting bacteriemia but probably was able to prevent blood-stream invasion if used early and effectively. Regarding spread, it was obvious that in cases treated early, within the first seventy-two hours, this treatment neither provoked nor retarded its occurrence.

In those cases treated late, after the end of the third day,

there were good reasons to believe that there was a greater likelihood of spread. If this is true, it is apparent that artificial pneumothorax should not be used in any case of lobar pneumonia after the third day.

In respect to postpneumonic complications, there was no evidence in adults that this treatment increased the likelihood of empyema except in those cases where such large injections of air were used that positive pressures were deliberately produced and maintained.

In addition to those factors which influence the mortality of lobar pneumonia under all previous forms of treatment, there is one more which must be taken into account when compression therapy is being considered. For this treatment to be effective, and it is useless unless artificial crisis is achieved, the pleural cavity must be free, otherwise the affected lobe or lung cannot be compressed. Either preexisting fibrous adhesions, recent adhesions, or both, render compression therapy futile.

In order to find out how often chronic fibrous pleural adhesions occur, we studied 515 autopsy protocols, kindly placed at our disposal by Dr. Krumbhaar, excluding all of those which recorded either acute or chronic pulmonary disease, except terminal bronchopneumonia. It was found that in adolescence the incidence of old pleural adhesions was about 25 per cent and that from the ages of twenty to seventy their incidence was about 50 per cent. In other words, there is only an even chance that therapeutic pneumothorax can provoke an artificial crisis in unilateral lobar pneumonia at the time of life when this treatment should be used. In an effort to explain Blake's mortality of 4 per cent in cases treated within the first seventy-two hours contrasted with his mortality of 55.5 per cent in cases first treated after this time, we reviewed 55 lobar pneumonia necropsy protocols. Many of those dying early in the disease had fibrinous or serofibrinous pleurisy, whereas many dying late had plastic pleurisy partially obliterating the pleural cavity and fibrous adhesions. It would appear therefore that after the third day new adhesions are frequently encountered which prevent adequate compression. Adding these to the pre-

dictable 50 per cent of preexisting chronic adhesions, the reasons become apparent for the futility of late treatment

Specific serum therapy is available for use in about 50 per cent of cases of lobar pneumonia. It is only effective when used early

Therapeutic pneumothorax used within the first seventy-two hours is capable of producing artificial crises in the same proportion of cases of *unilateral lobar pneumonia*, irrespective of the type of pneumococcic infection. Its place in the therapy



Fig 3—Case I Roentgenogram before treatment. Lobar pneumonia right lower lobe

of lobar pneumonia is established by this fact. When artificial crisis is achieved one is privileged to witness an artificial limitation of an otherwise self-limited disease.

During the past year we have treated 16 patients with lobar pneumonia by artificial pneumothorax, with 5 deaths, a mortality of 31 per cent. We hope that our own experience and that of others, whose reports we have analyzed and criticized, will persuade all of us to confine this form of treatment to *early adult unilateral lobar pneumonia*.

The following 3 cases from our series illustrate the production of artificial crisis on the third day of the disease



Fig 4.—Case I Roentgenogram after 800 cc of air Involved lung is completely surrounded with air and pneumonic lobe is compressed

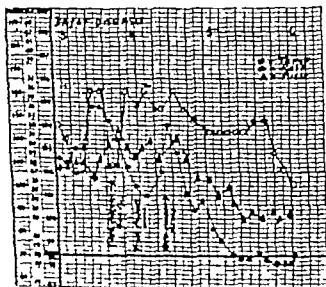


Fig 5.—Case I Clinical chart illustrating artificial crisis after first treatment and normal temperature early on the fifth day

(Case I) the futility of this treatment in the presence of pre-existing chronic fibrous adhesions (Case II), and the unjustifi-

able use of artificial pneumothorax on the sixth day of the disease (Case III)

Case I.—M C, female, aged thirty-eight, was admitted to the service of Dr Alfred Stengel on March 2, 1934, at 6 P M, on the second day of lobar pneumonia of the right lower lobe (Type I) Blood culture was negative She was given artificial pneumothorax as follows Four hundred cc on March 3rd at 11.30 A M., 400 cc. at 6 10 P M, and 350 cc. on March 4th at 11.30 A M Figure 3 is the roentgenogram before treatment, Fig 4 is the roentgenogram after two injections of air, and Fig 5 is the clinical chart showing the favorable response to treatment

Case II—A B, male, aged twenty-six years, was admitted to the service of Dr Alfred Stengel on January 8, 1934, at 2 A M on the second day of lobar

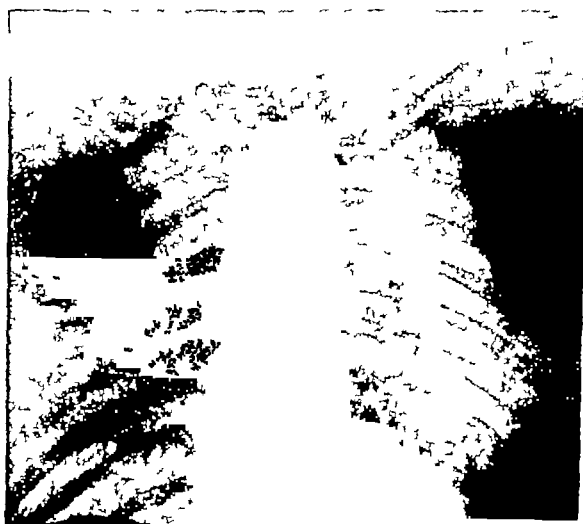


Fig 6—Case II Roentgenogram before treatment Lobar pneumonia of the right lower lobe

pneumonia of the right lower lobe (Type VIII) The blood culture was positive (6 colonies Type VIII per 2 cc) He was given artificial pneumothorax on January 8th at 4.30 P M After 200 cc of air had been injected, the patient complained of severe pain in the right chest This subsided and an additional 200 cc of air was injected A second injection at 11 A M on January 9th was discontinued after 250 cc of air because the intrapleural pressure was + 5 cm of water In view of obvious old adhesions, as indicated by pain and positive pressures, no further treatments were given There



Fig 7—Case II Roentgenogram after 650 cc of air in right pleural cavity. The lung is adherent to the lateral chest wall and the air is pocketed between the lower lobe and diaphragm. There is some air above the consolidated lobe.

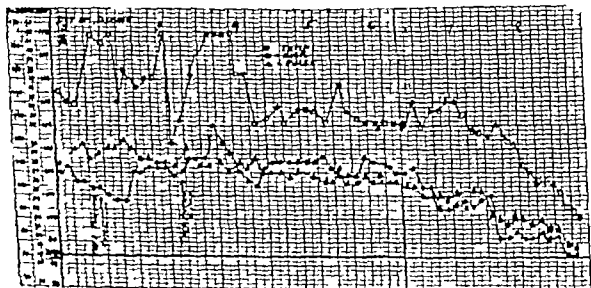


Fig 8.—Case II Clinical chart. Because of chronic pleural adhesions there was no effect on temperature or pulse after therapeutic pneumothorax. The increased rate of respiration after each treatment resulted from positive pleural pressures.

was no demonstrable effect from treatment. The clinical chart remained unaltered the temperature reaching normal on the eighth day.



Fig 9—Case III Roentgenogram before treatment Lobar pneumonia right lower lobe (Type III) sixth day of disease



Fig 10—Case III Roentgenogram after therapeutic pneumothorax 1000 cc, sixth day There is excellent pulmonary compression above and laterally but the lower lobe is firmly adherent to the diaphragm, probably because of recent adhesions

Case III.—J. M., aged thirty nine years, was admitted to the service of Dr Alfred Stengel on January 31 1935 at 3 p. m. on the fifth day of lobar pneumonia of the right lower lobe (Type III). The blood culture was negative. He was given 600 cc. of air in the right pleural cavity at 6.15 p. m. on February 1st (sixth day). The intrapleural pressure was -2 cm. of water after this treatment. Six hours later he was similarly given 400 cc. of air after which the intrapleural pressure was $+1$ cm. of water. There was no demonstrable effect on the clinical course. The temperature reached normal by crisis on the

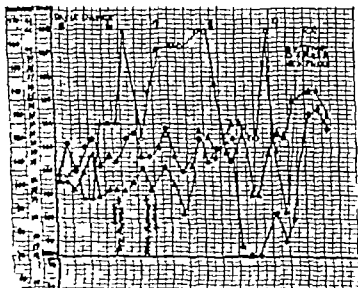


Fig. 11.—Case III. Clinical chart. There is no obvious effect from pneumothorax except an increased respiratory rate which followed each injection. Spontaneous crisis occurred on the eighth day. This was followed by contralateral spread and death on the ninth day.

eighth day. On the ninth day the left upper lobe became consolidated and the patient died. Necropsy revealed complete consolidation of entire right lung and early incomplete consolidation of the left upper lobe.

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SOME SURGICAL COMPLICATIONS OF PNEUMONIA

THE surgical treatment of postpneumonic lesions has for years provided a fertile field for surgical judgment and ingenuity. The epidemic of streptococcic pneumonia in March and April of 1918, and the epidemic of influenzal pneumonia in September, October and November of the same year with the resultant empyema which occurred following these infections, profoundly influenced current surgical practice and provided a renewed impetus for the study of the thoracic complications of pneumonia.

The high mortality attending rib resection, in the empyemas which occurred in these epidemics, demonstrated that surgeons in general were not conversant with certain of the important physiological considerations of the thorax, with which every surgeon doing thoracic surgery must be familiar, if he is to obtain the best possible results. Also the variation in the etiology of empyema, the marked variation from time to time in the virulence of a given infecting organism, and the varying response of thoracic tissues to different bacteria were not at that time generally appreciated.

In 1917, Ware¹ in a paper published from the Surgical Service of Doctor Howard Lilienthal suggested that the method of choice in dealing with acute empyema was through a long intercostal incision and wide exposure of the pleural space. Within two years from the time Ware had read his paper be-

fore the New York Academy of Medicine the Surgeon General of the Army had appointed an Empyema Commission to study the cause of the high death rate following operation for this disease in the Army camps, many of the deaths resulting from the adoption of the very principles enunciated by Ware in his paper. These observations demonstrate the lack of a fundamental knowledge of the many problems presented by a given lesion under varying conditions.

ACUTE EMPYEMA

It is of primary importance that the bacteriologic nature of the purulent effusion be determined prior to the adoption of any kind of surgical therapy. The fact that the streptococcus causes a thin effusion with a minimum of fibrinous exudate must constantly be kept in mind, for in such effusions the mediastinum is not made more rigid as it is in pneumococcal empyemas where a thick fibrinous exudate is the rule.

In the early stages of all acute purulent infections of the pleura the limiting adhesions between the parietal and visceral pleura are not well formed. This is especially true in the streptococcal infections where the fibrolysin of the streptococcus tends to prevent the localization of the infection.

If during this early period of pleural infection rib resection is done, the lung contracts, enlarging the empyema cavity and a more serious problem confronts the patient and the surgeon. The open thorax permits air to enter and be forced out with each act of respiration. The mediastinum, as Graham and Bell² have shown, swings back and forth reducing the efficiency of the opposite lung and putting an additional load on an already severely taxed circulation.

When frank suppuration has occurred drainage is indicated. Unless the patient is very ill and suffering from the effects of lung compression it is generally better, however, to wait until the pneumonic process is subsiding. The method by which drainage should be accomplished is often a matter of judgment. The sicker the patient the more important it is that a method for drainage be chosen which will disturb the patient as little

as possible. There is now more or less general agreement that of the operative procedures a closed method of drainage, at least at first, is the most satisfactory. Although aspiration without a doubt has a place in the early treatment of many empyemas it is frequently used beyond the period when it is indicated. As a method of cure it only rarely succeeds since it is impossible entirely to drain the collection by this method.

In general it may be said that in streptococcic infections of the pleura, air tight intercostal drainage is always indicated as the primary operation. In early patients who are very ill repeated aspirations may at times be indicated before interrib puncture. In pneumococcic empyemas we believe that air tight interrib puncture is also the method of choice in the early cases, reserving rib resection, or open drainage, for those cases which do not respond satisfactorily to the closed method of drainage.

Of the closed methods we have had very good results in both children and adults with the use of the Overholt modification of the Deryl Hart apparatus. With this apparatus it is possible not only to regulate the degree of suction which is desired but also to irrigate the pleural cavity with Dakin's solution provided a bronchopleural fistula is not present. We believe that this method of air tight interrib puncture under local anesthesia can safely be established if pressure symptoms exist within forty-eight to seventy two hours after the empyema has been diagnosed. Later when large fibrinopurulent masses form in the pleural cavity even though Dakin's solution is being used, rib resection may become necessary.

The advantages, however, of the closed method lie in the simplicity of the procedure, in the maintenance of more normal pressure relationships within the pleural space and in the fact that the negative pressure which can be maintained assists in bringing the lung out to the chest wall. The latter factor is of the greatest importance if a chronic empyema is to be avoided. A factor of equal importance in the immediate reaction of the patient is the slow decompression of the pleural collection. This is hardly possible when rib resection is prac

tised but it is easily accomplished by any of the air-tight methods, thus permitting the intrathoracic structures gradually to readjust themselves to the changing pressure relationships in the pleural cavity

Rib resection in our practice has therefore been reserved for those patients who fail to respond properly to the closed method of drainage. Even though the mediastinum may have become rigid so that the effects of a pneumothorax will not affect the opposite lung rib resection is not indicated until the lung has formed attachments to the parietal pleura so that it will not collapse with a subsequent large suppurating pleural cavity

Immediately after operation the patients are put on a high caloric diet which contains an adequate amount of protein. Children receive as high as 2200 calories a day and adults up to 4500 calories. There can be no doubt but that patients so treated do better. Respiratory exercises are encouraged during convalescence. While in bed the patient takes deep breaths at regular intervals and is encouraged to use the accessory respiratory musculature. Children are given balloons or clock spirometers and adults use either the familiar type of blow bottle or the conventional spirometer. As soon as the patient can get out of bed and can stand, a system of graduated setting-up exercises is begun. This is of the greatest importance in preventing and overcoming the postural deformities which are so frequently associated with pleural suppuration⁴

The improvement in the results now obtained in acute empyema is the result of a better understanding of the underlying pathology and pathologic physiology of the condition, a more general knowledge of the fact that the simplest operative procedure is the best for the primary operation, better selection of the time for operation, and more exacting care and attention to the postoperative treatment

INTERLOBAR EMPYEMA AND PULMONARY ABSCESS

An interlobar collection may be present with or without a pleural empyema. At times it may be difficult differentially to

diagnose an early interlobar collection from an abscess and this is even more difficult in those instances in which a fluid level can be visualized by x ray

In the majority of instances in the interlobar empyema, however, there occurs marked thickening of the interlobar pleura which points strongly to an interlobar collection. We have found that true lateral films as suggested by Fleischner² assist greatly in arriving at the correct diagnosis

It is now generally accepted that pulmonary infarction rarely occurs in pneumonia without associated cardiac decompensation. When infarction occurs one of two things may happen. The area may become organized or infection may supervene and an abscess develop.

The evidence that pneumococcic lobar pneumonia is a major etiologic factor in the production of lung abscess is not striking, although without doubt this association occurs occasionally. I must agree with Graham and his associates,³ who take exception to the statements of Hartwell⁷ and Hedblom,⁸ that pneumonia is the most important factor in the production of pulmonary abscess. While it is likely that in streptococcic pneumonia abscess may more frequently result the evidence even here is that pulmonary abscess of the surgical variety more frequently begins not in a primary pneumonic process but as a local necrotic lesion of the pulmonary tissue. In numerous instances, especially during the initial stages of abscess formation, it may be thought that the patient is developing pneumonia. It frequently happens, therefore, that the diagnosis of postpneumonic abscess is made when in reality the primary process was that of abscess and the surrounding lung reaction merely a part of the process which was associated with early abscess formation. We have at times been unable to distinguish between early abscess and lobar pneumonia except by repeated roentgenograms. The presence of a cavity with a fluid level which can be demonstrated by x ray, and the expectoration of pus are the two facts which help to clinch the diagnosis.

From the standpoint of treatment several facts are of con-

siderable importance The variation in the virulence of the infection and the variation in the reaction of the patient to the infection contribute to a widely varying clinical picture It is impossible to lay down any special rules for treatment for this will depend to a great extent upon the conditions met in a given patient It is generally recognized that the non-operative procedures—rest in bed, postural drainage and I would also include bronchoscopic aspiration—result in cure in a considerable number of patients The use of arsenicals in these cases has not proved very satisfactory in our hands and we do not employ this type of therapy at this time

This is not the place to discuss the operative treatment of abscess Suffice it to say that if after six to eight weeks of a good medical program no improvement results surgical intervention should be carefully considered In the interlobar collections operation is indicated Where there exists no pleural empyema the principles underlying the surgical drainage of a lung abscess should be adopted in order to prevent the infection of the pleural space

A high caloric diet to prevent tissue wastage is also of great value in the patients Frequently little attention is paid to the fact that Bell⁹ has demonstrated beyond dispute that in many of the patients with pulmonary suppuration the negative nitrogen balance may be as high as 21 Gm a day If these patients are to get well their tissues must be protected during the period that medical or surgical therapy is being carried out

In no other group of surgical cases is an active cooperation among internist, roentgenologist and surgeon so essential as in these patients with various types of pulmonary suppuration Where such cooperation is generously employed the end results are in general highly satisfactory Where it is ignored the mortality is high and the end results highly unsatisfactory The all too common chronic abscess and chronic empyema are too frequently the result of a poorly planned and executed therapy

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NUTRITIONAL ANEMIA

It has been our custom in the past to classify anemias under the heading of primary and secondary. More recently the various types are divided according to the size of the red cell and to the relative amount of hemoglobin contained therein, for instance, hypochromic microcytic and hyperchromic macrocytic. Most of the so-called secondary anemias, therefore, fall under the heading of microcytic hypochromic. One might say the most significant type of hypochromic microcytic anemia is the idiopathic or simple achlorhydric. The outstanding example of the macrocytic type of anemia is, of course, the addisonian or pernicious anemia, but, as we point out later, there are other conditions which one may include readily under this heading.

As a result of Castle's work the term "deficiency anemia," referring to the addisonian type chiefly, appeared in the literature. At present we find many diseases that may be grouped under the heading of nutritional anemia. Some of these might be named "deficiency anemias" as well. In using the term "nutritional" one assumes that the conditions classified under this heading occur as a result of some dietary lack, defect in the gastro-intestinal tract or as a result of faulty absorption of digested material.

Anemia is probably much more widely distributed than records show, and in all probability the conditions mentioned above play a prominent part in its etiology. It has been stated that during the first three months of life it is not uncommon

for the hemoglobin to fall as low as 60 per cent. This has been set forth in the past as a physiological anemia. It seems more likely, however, that the cause of this reduction lies in a nutritional defect. From blood counts taken on supposedly normal students at different periods of the year we have noticed that many of them have a moderate anemia, particularly during the latter months of the school year.

The simple anemia of pregnancy has long been termed a physiological anemia, and although we know that there is an increase in blood volume, it seems reasonable to suggest that this anemia may result from defective dietary conditions in certain patients. Support for this statement is found in the fact that a more severe form of hypochromic microcytic anemia due to nutritional factors and a very severe form occurs in the latter months of pregnancy, known as the pernicious anemia of pregnancy also the result of certain deficiencies.

It has been pointed out for many years that an anemia develops in the chronic arthritic and in the chronic nephritic. We know, too, that an adequate protein diet has not been administered to many of these patients, just as a low protein intake has been set forth as the ideal diet during pregnancy.

One might divide these nutritional anemias into specific and nonspecific. Under the specific nutritional anemias of macrocytic hyperchromic type are included the following conditions, in which there is a known defect in the intrinsic factor or a deficiency in the extrinsic factor, or a deficiency in the storage of the combination factor:

- 1 Addisonian or pernicious anemia
- 2 Sprue
- 3 Pellagra
- 4 Pernicious anemia of pregnancy
- 5 Fish tapeworm infestation
- 6 Subtotal and total gastrectomy
- 7 Gastric polyposis
- 8 Tropical macrocytic anemia

Under the nonspecific nutritional anemias of macrocytic hyperchromic type are included the following conditions, in

which the intrinsic factor is present and the extrinsic factor cannot be utilized

- 1 Gastrocolic fistula
- 2 Multiple intestinal anastomoses
- 3 Multiple abdominal adhesions
- 4 Prolonged chronic diarrhea
- 5 Idiopathic steatorrhea (celiac disease)
- 6 Intestinal stenosis

Under the heading microcytic hypochromic specific nutritional anemias might be placed

- 1 The severe anemia of pregnancy
- 2 The idiopathic hypochromic anemia
- 3 The Plummer-Vinson syndrome
- 4 Certain cases of pellagra and sprue

Under the nonspecific nutritional anemias, which are also microcytic hypochromic, might be placed

- 1 The anemia of the infant.
- 2 The anemia of the average individual
- 3 The anemia of chronic arthritis and chronic nephritis
- 4 The simple anemia of pregnancy

Mechanism—Addisonian anemia is the outstanding example of the macrocytic nutritional anemias. As was pointed out by William Pepper in 1875, and later emphasized by Cohnheim, Ehrlich, and Rindfleisch, the bone marrow in pernicious anemia is hyperplastic and megaloblastic. The megaloblasts, which normally are present in numbers of less than 1 per cent of the erythropoietic elements, are found to be greatly increased in this disease. There is also an increase in the erythroblastic and normoblastic elements. During the relapse stage of this condition practically all the fat is replaced by these erythropoietic elements. Although there is this excess in the bone marrow, a dearth of red cells occurs in the circulating blood. This state has been described as a maturation arrest. Some substance is lacking which ordinarily stimulates the primitive red cells to develop into normal cells. It has been pointed out by Minot, Murphy, Whipple, Sturgis, Morris, *et al*, that the administration of certain substances to these patients, if ab-

sorbed in sufficient quantity and utilized in the body, causes these primitive red cells to mature and become normal red blood cells, which enter the circulating blood. The first evidence of this phenomenon can be demonstrated by enumerating the number of reticulocytes in the circulating blood from three to ten days after the administration of effective substances.

The reticulocyte response is an expression of the effectiveness of any of the several forms of treatment. The result may be expressed in percentage, that is the number of reticulocytes per 1000 red blood cells, but is better set forth as the number in relation to the total erythrocyte count. As a rule the lower the red blood cell count, the greater the reticulocyte response when expressed in percentage. It has been pointed out by Bethell,¹ however, that in some instances the reticulocytes will be thrown into the blood stream over a longer period, although the peak of the curve is not as high as that reached in other cases with similar expectancy in reticulocyte response. Should we express these two responses in terms of percentage alone, one might assume that the substance producing the lower percentage of reticulocytes was not as active as that which produced a greater response. If the total number is estimated, one finds that the two responses are comparatively similar.

Stomach—In 1877, Fenwick² described the association of atrophy of the stomach with fatal anemia. Henry and Osler³ in 1886 were the first to describe accurately the gastric pathology. Following this the association of gastric change with addisonian anemia was generally accepted. In 1886 Cahn and Mehring⁴ established the fact that free hydrochloric acid was absent in these patients. Discussion arose as to whether the anatomical changes and the lack of free hydrochloric acid preceded the development of the anemia or whether it was merely a part of the picture and perhaps entirely secondary to other aspects of the disease. We know that achlorhydria has been observed as long as fourteen years before the development of the anemia. Dr Martin Rehfuss has a record

of several patients whose free hydrochloric acid was absent from eleven to thirteen years before they developed other evidences of pernicious anemia

It was pointed out by Hunter that mouth infection was present in most of the cases of pernicious anemia, and he concluded that the swallowing of this infected material produced atrophy of the gastric mucous membrane. Others assumed that alcohol, which is known to produce atrophic change, was responsible for the condition of the stomach in these patients. However, many of the patients with pernicious anemia did not use alcohol, and some of them did not have mouth infection.

During all this discussion the point of importance was overlooked, and it was not until 1929, when Castle⁵ made his brilliant discovery, that we were aware of a substance in the gastric secretion which is possibly the most important factor in the development of the addisonian anemia. Castle, with a tube in his stomach, ingested beef muscle. After digestion with his normal gastric juice, the material was removed and passed into the stomach of a patient with pernicious anemia. It was found whenever this procedure was followed day by day that a reticulocyte response occurred similar to that which followed the administration of liver or liver extract. Beef muscle was then incubated with free hydrochloric acid and given to pernicious anemia patients without any material response. Following this, normal gastric juice was incubated with beef muscle and given to pernicious anemia patients, adequate reticulocyte response resulted. Castle then postulated the theory that there was in the gastric juice of normal individuals an "intrinsic factor" which acted upon certain foods and produced a substance which when absorbed brought about the normal maturation of the red cells of the bone marrow. It has been pointed out that this so-called "intrinsic factor" bears no relation to the pepsin content, the rennin content, or even the hydrochloric acid content of the stomach, and in individuals in whom no free hydrochloric acid is present the intrinsic factor may be present in normal amounts.

Griffiths⁶ stated that when beef protein is fed to the patients with addisonian anemia there is a deficient digestion of that food. It has been suggested by Hurst⁷ that such imperfect protein digestion products in the intestinal tract might liberate hemolytic and toxic factors as a result of abnormal bacterial activity. He stated further that there was an excessive number of bacteria due to the absence of the normal antiseptic action of the gastric juice. Davidson⁸ however, has not supported this view, and recent studies have led Hurst⁹ to modify his theory. Ratner and Gruehl¹⁰ pointed out that proteins may enter the blood stream from any part of the bowel, even as low down as the rectum. The defensive measures against the entrance of proteins are the general impermeability of the intestines, the digestive enzymes, specific antibodies in the circulating blood, and the ability of the kidneys to eliminate protein material. The failure of these mechanisms permits antigens to enter the blood stream in sufficient amounts so that the individual may become profoundly sensitized, and on the ingestion of amounts of the antigen in the future, marked allergic manifestations result and sometimes even death. Protein digestion is impaired in pernicious anemia. When these improperly split protein materials pass into the intestinal tract and are absorbed, the result should not be overlooked, even though it cannot be evaluated at this time. It might be well at this point to review some of the theories and practices that were applied and utilized in the past in the treatment of addisonian anemia.

In Retrospect—The gastro-intestinal tract has long been implicated as a position from which etiological factors might arise that were of significance in the development of pernicious anemia. The large intestine was considered a possible focus and appendicostomy was performed, with flushing of the tract, supposedly cleaning out toxic materials and thereby preventing the development of the disease. An operation was performed of short-circuiting the colon, uniting the ileum with the sigmoid. Reports of improvement following this operation were presented.

As the liver is frequently enlarged, and as we find the icteric tinge, the increase in bilirubin in this disease, it was not to be unexpected that someone would suggest the removal of the gallbladder. This was done, and in a certain number of instances the streptococcus was found in the gallbladder, and seemingly these patients were improved.

Bacteria came in for their share of etiologic consideration. The streptococcus received a great deal of attention. The bacillus of Welch was found to be tremendously increased in number in this disease. Following this observation, antitoxin was administered in such quantities that the supply became limited, however, without any particular beneficial result.

Experimental work in the monkey showed that if the organism and toxin were taken by mouth, an anemia was produced in some instances that was not typical, but if a lesion was developed in the stomach and the material ingested, an anemia resulted resembling in some respect that seen in the pernicious anemia patient. The colon bacillus and other organisms were held responsible by certain observers for the development of the condition. It was pointed out that in patients with achlorhydria in which pernicious anemia never developed, the content of intestinal flora and particularly the bacillus of Welch was tremendously increased.

Another phase of the etiology and treatment of this disease was in relation to the blood stream. Some observers reported splendid results following the injection of mercurochrome, others metaphen and aniline-gentian violet. It was pointed out that a type of bean sprout would not grow as well in pernicious anemia serum as it did in the serum of the normal individual.

The suggestion was made that the absence of free hydrochloric acid was the chief factor in the production of the disease, and there were some who stated that the absence of free hydrochloric acid was simply part of the disease picture.

Transfusion, of course, was used in this condition. Large doses of blood were given at weekly or bimonthly intervals without permanent improvement. Later smaller doses of blood

were administered more frequently and a certain number of patients were affected favorably and carried over long periods of time comparatively well. This procedure at the present time is not indicated except in a few aberrant cases in which no other form of treatment seems to be of benefit.

Splenectomy—In some of the patients with pernicious anemia the spleen is enlarged, and so splenectomy came into vogue as a method of treatment. Another reason for the operation was that as the spleen is the so-called "graveyard" of red blood cells, it was thought to remove the graveyard and the red cells would live longer and prosper.

Present Day Facts Concerning Etiology and Treatment—Not long after liver extract was developed by Minot and Cohen, *et al*,¹¹ and about the same time that Castle performed his experiments on the use of normal gastric juice and beef muscle, Sturgis¹² showed that chopped hog's stomach when given to individuals with pernicious anemia produced a reticulocyte response and red cell and hemoglobin increase comparable to that induced by adequate liver therapy. It was found that when kidney, pancreas, and brain was fed, responses occurred which suggested that these other organs contained an effective substance present in small amounts only. The material obtained from the hog's stomach was later refined and has been put on the market under the name of ventriculin. Each ampoule of ventriculin contains 30 Gm, which is equivalent to 200–300 Gm of hog's stomach. This dose is the equivalent of 12–14 Gm of liver extract.

Morris¹³ in 1932 reported the use of a concentrated extract of hog's gastric juice. When injected, 5 cc to 8 cc of the material was equivalent to 3200 cc and 5700 cc respectively of the gastric juice of hogs. This material when injected stimulated a reticulocyte response which persisted from thirty to forty-four days. Hemoglobin and red cells were increased and remained normal for a considerable period of time. Morris designated this substance, which was found to be heat labile, dialysable, and able to withstand chemical treatment known to destroy enzymes, as addisin. Later Connor¹⁴ concentrated

normal human gastric juice and obtained a result in addisonian anemia similar to that reported by Morris. It was first thought that the injection of this material (addisin), which might be simply a concentrated form of the intrinsic factor, produced a reaction of the intrinsic factor and the human muscle at the site of injection. However, later investigation failed to reveal any evidence of necrosis or pathologic change, and then it was assumed that such a reaction might take place at some remote source. Minot noted that fever and chills accompanied the injection of the material and that the reticulocyte response was similar to that obtained by injections of arsenic, which were used as one of the older forms of treatment of the condition. Morris *et al*, however, have been able to eliminate most of these unfavorable reactions by the use of an acetone extract of gastric juice.

Wilkinson¹ demonstrated that human gastric juice when neutralized previous to vacuum distillation would not bring about a reticulocyte response. However, the neutralization may have destroyed or inactivated the hematopoietic substances.

The material in normal human gastric juice which can be made active by vacuum distillation does not pass through ultrafilters. The intrinsic factor is present at the onset of the vacuum distillation preparations. The material in gastric juice after vacuum distillation which is active when injected is not identical with the intrinsic factor because this factor is destroyed or used up during the process of vacuum distillation, at which time the active material in concentrated gastric juice is formed.¹⁰ The ultrafiltrate of gastric juice free of pepsin, rennin and mucin, but containing the intrinsic factor, is not active after vacuum distillation. This tends to support the hypothesis that the stimulating material in human gastric juice is not formed unless both intrinsic and extrinsic factors are present in the gastric juice during vacuum distillation.

Fouts *et al*¹⁷ found that human gastric juice was inactive on intramuscular injection when concentrated at ice-box tem

perature by ultrafiltration, but when this material was diluted with water and reconcentrated by vacuum distillation at 40° C it was found to be potent. Fresh gastric juice seemed to be inactive. Storing this material on ice for several months, and then concentrating it, a substance was formed which was effective. It would seem that before a normal gastric juice can become potent some reaction must take place which proceeds rapidly at 40° C, but slowly at ice-box temperature, and, in addition, when the temperature exceeds 60° C, the reaction does not occur. One might conclude from these results that gastric juice contains both the intrinsic and extrinsic factors, which interact to form a hematopoietic agent during the process of vacuum distillation.

The extrinsic factor, as suggested by Klump and Koletzky,¹⁸ may be derived either from the protein of gastric mucin or cellular debris. One of the men working with Wearn at the Lakeside Hospital reported a reticulocyte response from the instillation into the stomach of a pernicious anemia patient of a large amount of the gastric juice of a cow. Klump has demonstrated a hematopoietic response from the gastric juice of dogs when injected into rabbits. Miller and Rhoads¹⁹ stated that the gastric secretion of dogs had no hematopoietic power.

Barnett²⁰ reports cases of the achylia gastrica without anemia in whom no intrinsic factor could be found. Klump, however, states that the intrinsic factor was demonstrated in individuals with achylia gastrica without anemia and in three patients with hypochromic anemia who responded to iron but not to liver therapy. Barnett also described a patient with typical addisonian anemia who possessed gastric juice normal in volume and acidity and high in content of the intrinsic factor.

Castle²¹ feels that the effect may lie in an inadequate absorption of the antianemic factor, even though elaborated in adequate amounts. Castle²² reported two patients with pernicious anemia in which the gastric juice was apparently normal, but the intrinsic factor could not be demonstrated.

The *intrinsic factor* seems to be secreted by the gastric mucosa, is organic in nature, thermostable, neither acid, pepsin nor rennin, but possibly an enzyme

Bloomfield and Polland²³ have followed twenty three patients with no free hydrochloric acid from one to seven years. The patients were carefully chosen and had no evidence that suggested the diagnosis of pernicious anemia or hypochromic anemia, cancer of the stomach or marked gastrointestinal symptomatology. In no instance was there evidence that the absence of gastric secretion to histamine stimulation led to the development of any unusual symptoms or impairment in health. Cancer, hypochromic anemia or pernicious anemia did not develop. There were two patients, not included in this group, who developed evidences that suggest that they might be early cases of pernicious anemia. One of the patients after two years seemed perfectly well.

Bloomfield states that it is improbable, if not impossible, that patients with unexplained anacidity were able to secrete the intrinsic factor, at least in quantity that can be of value. Extraction of stomach contents after a meal of beef muscle shows that the food is improperly digested. Two patients with unexplained anacidity, in whom Barnett failed to demonstrate the intrinsic factor in 1931, have been followed to date without showing any signs of pernicious anemia.

These studies, some of them controversial, emphasize the point that what seems to be a simple explanation of the part the stomach and certain substances in the gastric juice play in the etiology and treatment of pernicious anemia, is not simple, but quite complex. Moreover, there are patients with pernicious anemia who do not lack the intrinsic factor, but show only a reduction in the amount of the intrinsic factor. It has been noted that the gastric juice of these pernicious anemia patients, interacted by beef muscle, produced a reticulocyte response comparable to that which was brought about by the interaction of normal gastric juice and beef muscle, with the exception that the reticulocyte count was lower than normal expectancy.

Achlorhydria in Conditions Other Than Pernicious Anemia—The occurrence of achlorhydria is much more common than is generally thought. Some of these cases may be the result of improper gastric analysis, others due to the fact that histamine is not used in conjunction with the test or as a second test to determine the absence of the free hydrochloric acid. It has been set forth that from 8 to 15 per cent of normal individuals show an absence of free hydrochloric acid. We know that free hydrochloric acid is absent in certain patients during the acute stage of hyperthyroidism. In most of these the acid returns to normal or nearly normal, if the thyroid condition receives the proper treatment. In many infections free hydrochloric acid is low or absent. In arthritis of the infectious or deforming type we find many instances of an absence of free hydrochloric acid. The same is noted in certain cases of neuritis. In pregnancy free hydrochloric acid has been reported to be absent in as many as 50 per cent of the cases, and, of course, following the prolonged use of alcohol we may find an absent or deficient free hydrochloric acid with changes in the gastric mucosa.

These findings emphasize the point that although free hydrochloric acid is absent in the great majority of patients with pernicious anemia, it is not the important factor, in fact there have been cases of this disease reported in which the free hydrochloric acid was present in normal quantity, and, furthermore, cases are on record showing that after adequate treatment free hydrochloric acid has returned in small or adequate amounts.

Special Features Concerning the Various Substances Which Are Effective in the Treatment of Pernicious Anemia—Herron and McElroy²⁴ explain the increased potentiation of autolyzed liver on the basis that there is hydrolysis of nucleoproteins of the liver by the autolytic enzymes which are present in every cell, as well as in the stomach, and differ from the proteolytic enzymes—pepsin and trypsin—in that the latter only slightly effect nucleoprotein. These writers claim that the increased potency

of the liver preparation is as effective as the liver extract for parenteral use Klump and Koletzky, however, noted an increase in potency, but not of sufficient degree to make it comparable in effect to liver extract for parenteral use

Three hundred Gm of liver yields 12 to 14 Gm of liver extract. Two hundred to 300 Gm of hog's stomach yields 30 to 40 Gm of stomach extract This is the minimal amount necessary to produce a maximal reticulocyte response.

Reimann²⁵ has noted a thirty fold increase in the potency of whole liver when digested in normal gastric juice He found that 10 Gm of whole liver digested with 10 cc. of gastric juice was sufficient to produce a maximal reticulocyte response in a patient with pernicious anemia Barnett and Thebaut,²⁶ however, were unable to obtain such an increase Four and a half Gm of liver extract incubated with 50 cc. of gastric juice has been found to produce a maximal reticulocyte response when fed to patients with pernicious anemia.²⁷

Liver stomach Mixtures—Fresh hog's liver was ground and mixed with ground fresh hog's stomach The extract evaporated in vacuum, the resultant preparation exhibited a potency of three to four times that of raw liver Treating liver extract with fresh ground hog's stomach yielded a substance which was also three or four times as potent This material was used in pernicious anemia cases and the value of given preparations was determined by the reticulocyte peak, increase in red corpuscles, the general improvement of the patient, and compared with the effect exerted by 225 to 250 Gm of raw liver, or 300 Gm of stomach, or a vial of liver extract No 343 One might assume that these results were simply an additive effect, but this is not the case, as the clinical results indicate that one third to one-seventh of a unit dose of liver treated with one-tenth to one-thirtieth of a unit dose of stomach exerts an effect equal to that of a unit dose of liver or of stomach²⁸

One must assume that there are two substances in the liver, that is the *extrinsic factor* and the *active principle* In extracting there is considerable loss of extrinsic factor rather

than a loss of active principle The increase in potency of liver and liver extract when treated with normal gastric juice is similar to that obtained when human gastric juice is allowed to act on beef muscle rather than to an actual increase in the active principle, originally present in the liver This would indicate that the active principle, although lost, can be made up because of the presence of the extrinsic factor in the liver substance, which when acted upon by the intrinsic factor produces again the active principle

The use of $4\frac{1}{2}$ Gm of liver extract can be utilized to determine the amount of the intrinsic factor present in gastric juice, for we know that if $4\frac{1}{2}$ Gm of liver extract is incubated with 10 cc of gastric juice a small reticulocyte rise will occur One might, therefore, express in terms of units the amount of intrinsic factor in each 10 cc of gastric juice until the maximum reticulocyte response is reported A similar suggestion was made by Fouts

Barnett²⁰ reported that the use of gastric juice from pernicious anemia free individuals with achlorhydria when incubated with beef muscle failed to produce an adequate reticulocyte response His experiments, however, are not conclusive

Intra-osseous Injection of Liver Extract—Josefson³⁰ states that with a special apparatus he aspirates 4 cc of bone marrow and then injects 4 cc of liver extract into the bone-marrow cavity in cases of pernicious anemia He has used this in 23 patients The therapy is repeated in one to three months We have used the injection of liver extract 3 cc in several cases of atypical anemia of the macrocytic type which did not respond to other forms of treatment and sealed the material in with Horsley's wax, but no good results were obtained Our results cannot be considered to be a fair trial of Josefson's method as the cases we studied probably were not pernicious anemia Further studies in a large group of cases are necessary before this method can be considered as satisfactory or more satisfactory than the other methods in use at the present time

Nature of the Extrinsic Factor—The extrinsic factor is found in food such as beef muscle, eggs, autolyzed yeast, rice polishings, wheat germ and liver, and reacts with the intrinsic factor to form a thermostabile antianemic principle, which is absorbed and stored in the liver and kidney and probably in various other tissues. Shortly after Minot and Murphy brought out their original communication, Maurer and Kessel published results obtained in a series of pernicious anemia cases, with a special diet which included liver, wheat embryo extract, and brewer's yeast. They suggested that the effect might be due to the presence of vitamin B. A great deal of work has been done with this point in view since that time, and it has been suggested that the extrinsic factor is vitamin B complex, or at least related to it. Vitamin B is of a very complex nature and is made up of a number of substances—B₁, B₂ or G, and others. It is interesting to review some of the results obtained by various workers, using products containing the vitamin B complex.

Larnum²¹ reported a decrease in volume and acidity of gastric secretion in Pavlov pouch dogs who were fed a diet autoclaved in an alkaline medium which destroyed the antineuritic factor. Cowgill²² demonstrated gastric achlorhydria in dogs that received food lacking the vitamin B complex. Webster and Armour²³ stated that gastric secretion was restored by powdered and autoclaved yeast and lost when these materials were withdrawn. Ungley and James²⁴ tested the effect of yeast and wheat embryo extract in anemias in an effort to determine the nature of the hematopoietic factor in yeast that was effective, particularly in pernicious anemia. They suggest as a result of previous work with the yeast and wheat germ preparations that these extracts may owe their potency to the presence of the extrinsic factor or the presence of a breakdown product of the extrinsic factor, resulting from the interaction with an enzyme liberated during autolysis or due to a substance resembling the liver active principle.

Various yeast fractions²⁵ were administered orally, rectally or by intramuscular injection in 13 cases of pernicious anemia.

To one patient, a female, aged fifty-two, whose red cells were 1,720,000, hemoglobin 49 per cent, color index 1.2, white blood cells 5000, reticulocytes 3 per cent, an alcoholic extract from 8 ounces of marmite was given each day in divided doses per rectum, 54 ounces were administered in all. The result as far as reticulocytes or red cell increase was negative. The subsequent daily administration of the alcoholic extract from 4 ounces of marmite by mouth resulted in a moderate reticulocyte response, and the return of the red cell count and hemoglobin to normal on the eightieth day.

Thirty cc³⁴ derived from 300 Gm of baker's yeast, containing the total available quantity of vitamin B₂ was given to a patient with pernicious anemia over a period of seven days. At the start the red blood cells were 1,380,000, hemoglobin 36 per cent, color index 1.3, white blood cells 3400, reticulocytes, 0.6 per cent. No results were obtained. Fifty cc were then given daily for ten days. There was an increase of the reticulocytes to 6.4 per cent, but a drop in red cells occurred. An alcoholic extract of 120 Gm of marmite was administered daily at this point and the reticulocytes rose to 27.2 per cent and the red cells on the eighty-ninth day to 5,120,000 and hemoglobin 97 per cent. One might explain the action of the marmite in this case as being the result of the interaction of a certain amount of intrinsic factor in the gastric secretion of this patient with the marmite.

To a female,⁸⁴ aged fifty-three, suffering from pernicious anemia of two years' duration, a yeast extract following the same formula as is utilized in the manufacture of liver extract was administered in daily doses derived from 480 Gm of yeast. The red blood cells were 1,380,000, hemoglobin 42 per cent, color index 1.45. The reticulocytes rose to 7 per cent on the sixth day and there was a small increase in red cells and hemoglobin. A yeast extract, prepared according to the formula for the preparation of intramuscular liver extract, was given in amounts derived from 100 Gm of yeast. There was no result. This experiment was to determine whether or not there was a substance present in yeast extract similar

to that in liver extract for peroral and parenteral administration, namely liver active principle.

To a patient,³⁴ aged fifty-six, with pernicious anemia of two years' duration and some neurologic phenomena a 65 per cent alcoholic extract derived from 480 Gm of fresh brewer's yeast was administered daily for ten days. The red cells were 1,260,000, hemoglobin 34 per cent, reticulocytes 2 per cent at the onset of treatment. The reticulocytes reached 7 per cent on the eleventh day, the hemoglobin was increased by 10 per cent, and there was slight increase in the red blood cell count. The patient, however, showed no subjective improvement. Following this for ten days he received similar doses of the 65 per cent alcoholic extract which had been allowed to autolyze, but there was no secondary reticulocyte rise, although on the twenty-sixth day the red cells were 1,740,000, hemoglobin 49 per cent. Liver extract was administered at this point, resulting in a reticulocyte rise to 10.4 per cent, followed by increase in red cells and hemoglobin. This experiment was to determine whether or not material potent for pernicious anemia may arise or increase during the autolysis of the yeast. The results indicate that there is, at least in this instance, no increased potency after autolysis. As pointed out previously, autolysis of liver increases its potency.

A male,³⁴ aged thirty five, suffering from pernicious anemia, atypical in the fact that free hydrochloric acid was present in small amounts in the gastric juice after histamine stimulation, received daily an alcoholic extract of fresh yeast derived from 480 Gm. The reticulocytes rose to 22.2 per cent on the sixth day, and the red cells and hemoglobin increased in the regular manner. He was now given an extract prepared from yeast of the same batch, but it had been allowed to autolyze for three weeks before extraction. The hemoglobin and red cells continued to rise, but there was no secondary reticulocyte increase, although the reticulocytes did rise from 1.2 to 3.4 and the red cells and hemoglobin continued to rise. Various other substances were used—marmite and an alcoholic extract from

marmite—and on the sixty-first day the red cells were 3,920,000, hemoglobin 74 per cent. Liver extract and whole liver were administered from this point on. This result is of sufficient magnitude to be considered as evidence that the material used was effective.

I do not think that we can say that substances other than the alcoholic extract from fresh yeast did or did not act because the progress seemed to be continuous and it does not seem possible that the administration of alcoholic extract or fresh yeast alone could be responsible for such a long continued good result. Other cases studied showed that an alcoholic extract of yeast, given intramuscularly to a patient with pernicious anemia, gave a negative response. When the material was given by mouth a moderate reticulocyte response was followed by increase in hemoglobin and red cells. Another patient received an alcoholic extract from autoclaved marmite—120 Gm daily without effect and 65 per cent alcoholic extract of marmite—120 Gm daily without effect, but later responded to daily injections of liver extract. Another patient received alcoholic extract of yeast intramuscularly without result, which was followed by a moderate response when the same extract was given by mouth. Another patient received the complete alcoholic precipitate or 1920 Gm of yeast by mouth with a reticulocyte rise, but no increase in the hemoglobin and red cells. Following this liver extract was given and resulted in the reticulocyte response to 14 per cent and followed by increase in other blood elements.

In his discussion Ungley points out that the administration of a 65 per cent alcohol-soluble fraction of marmite in doses derived from 120 Gm daily resulted in a moderate response in one patient, a good result in another, but subsequent experiences were less satisfactory.

The experiments to determine if autoclaving increased the potency of the marmite in pernicious anemia were not satisfactory. Strauss and Castle³⁵ have pointed out that the extrinsic factor in autolyzed yeast is not readily destroyed by autoclaving. In one of Ungley's cases two vitamin B₂ con-

centrates derived from baker's yeast by lead acetate precipitation gave only slight reticulocyte response compared with that obtained from an alcoholic extract of marmite. The two concentrates seemed to have the same B_{12} effect on rats. This suggests that there is no parallelism between vitamin B_{12} potency and hematopoietic effect, and suggests that the factor in marmite effective in pernicious anemia is not vitamin B_{12} . Wills has demonstrated that the factor in marmite effective in tropical macrocytic anemia is not vitamin B_{12} . Egg white, although rich in vitamin B_{12} , is not effective in pernicious anemia when incubated with normal gastric juice, administered by mouth.

Diehl and Kuhnow³⁰ reported three patients treated with vitamin B_{12} preparations which had been exposed to the influence of normal gastric juice. There was a slight reticulocyte rise, but no increase in red cells or hemoglobin. Furthermore, during the administration of the vitamin B_{12} alone, no reticulocyte rise was noted. It is of interest that the 65 per cent alcohol soluble fraction of fresh brewer's yeast used by Ungley showed very little vitamin B_{12} activity when tested in rats.

The Autolysis of Yeast—Dried yeast and unautolyzed baker's yeast showed no hematopoietic effect. Marmite, which is an extract prepared from brewer's yeast after autolysis in salt solution, was active, as stated above. This suggests that there may be an activation of the extrinsic factor by an enzyme liberated from the yeast during this process. Further experimentation, however, did not support this contention. Autolysis with $\frac{1}{10}$ normal hydrochloric acid, as described by Herron and McElroy,³¹ which is said to have greatly increased the potency of liver for blood regeneration, was applied to fresh brewer's yeast, but the result was inconclusive.

It may be that the effect of yeast preparations in pernicious anemia is due to the extrinsic factor, which probably interacts with traces of the intrinsic factor in patients' gastric juice. It is suggested that many patients with pernicious anemia, although showing achlorhydria, secrete the intrinsic factor in the gastric juice in small amounts, which can unite with the

extrinsic factor of yeast. The extrinsic factor is present in autolyzed yeast in approximately twenty times the concentration found in beef muscle. It is also present in rice polishing and wheat germ³⁸. Whole hen's egg contains small amounts of the extrinsic factor. With regard to its presence in the animal tissues, it is important to note the potency of liver extract, if increased by incubation with the known sources of the intrinsic factor, such as gastric juice or stomach tissue³⁹.

Musser⁴⁰ pointed out the clinical relationship between pellagra, sprue and pernicious anemia in the phenomena found in the gastro-intestinal tract and tongue. The glossitis may be present with normal secretion, and, as was pointed out by Lewis,⁴¹ the absence of an intrinsic factor occurred without tongue manifestations. Cohn⁴² reported essentially negative results in feeding 120 Gm of yeast daily and with various concentrates of vitamin B.

Strauss and Castle⁴³ and Davidson⁴⁴ found autolyzed yeast alone to be inert in the treatment of pernicious anemia. The autolyzed yeast was vegex, and Castle thought that marmite might contain the extrinsic factor or an extrinsic factor which vegex did not. Using autolyzed yeast and vegex incubated with normal gastric juice and vegex after autoclaving for five hours to destroy vitamin B₁ or an 80 per cent alcoholic extract of vegex, it was found that in doses equivalent to 12 Gm of marmite each of these mixtures produced typical reticulocyte response and remissions in pernicious anemia. They concluded that the extrinsic factor was a substance related to vitamin B₂, if not vitamin B₂ itself. It was pointed out that the protein extract of washed beef muscle used by Castle as the source of the extrinsic factor was rich in vitamin B₂⁴⁵.

Commercial liver extracts and stomach preparations contained vitamin B₂⁴⁶. Since liver extract No. 343 is rich in vitamin B₂, as pointed out in a communication from Cowgill to Klump, the increase in potency of this extract when incubated with hog's stomach is said to be explained.

Wills⁴⁷ believes that the use of 80 per cent alcohol would inactivate or destroy vitamin B. Dried brewer's yeast and

watery yeast extract and egg white containing doses of vitamin B₂ seven times that of marmite all failed to produce results in patients with tropical macrocytic anemia, who then responded to marmite. She concluded that the autolysis broke down some of the protein into simpler products and that the marmite probably owed its properties to one of these. Lassen and Lassen⁴⁸ conclude from their experiments that yeast appears to be rather completely without an antianemic effect or contains minimal amounts of antianemic factor. On the addition of normal gastric juice they were not able, with any degree of certainty, to ascertain increase in the content of active antianemic principle. This whole subject remains in its present uncertain state.

The Storage of the Liver Active Principle—Richter, Ivy, and Kim⁴⁹ concluded that the active principle was not an integral part of liver tissue, but a storage product which could be released when needed. Goldhamer, Isaacs, and Sturgis⁵⁰ concluded from their experiments that the active principle is present in the liver at least two months before birth. It may, however, be present before this. The active principle may be absent from the liver of an inadequately treated case of pernicious anemia. This active principle is present in the liver of an adequately treated case. The cirrhotic liver of a patient may not contain the active principle, particularly if this patient has developed an anemia during life. The liver may be sufficiently damaged so that the active principle, although present, cannot be presented to the tissues for utilization. A pernicious anemia like blood picture may occur if the liver cannot store the active principle or cannot present it to the tissues for utilization. They conclude that the active principle is a storage product and not an intrinsic part of the liver. Wintrobe and Shumaker⁵¹ state that the macrocytic anemia is usually only moderate in degree. A clear-cut response to liver therapy is not the rule, but does occur occasionally. They suggest that the product produced by the interaction of the extrinsic and intrinsic factors may be

inadequately stored, or that the liver disturbance may interfere with the utilization of the stored product

Active Principle Storage in the Liver, Experimental

—Miller and Rhoads¹² found that they were unable to produce a condition in dogs that resembled the clinical pernicious anemia. They were able to produce black tongue, but not an achlorhydria. Swine were fed on the diet, as noted in Table A in Miller and Rhoads' article. In order to ascertain the effect of a deficiency of vitamins other than the vitamin B complex, swine similar to those in a major experiment were kept under similar conditions and fed a diet which was vitamin deficient, but otherwise adequate. The swine on the experimental diet (Table A in Miller and Rhoads' article) developed a symptom complex similar to the canine black tongue, but not identical. Stomatitis, achlorhydria, diarrhea and anemia, loss of appetite and weakness occurred. In some instances a macrocytic anemia was produced, in others a microcytic. Controlled animals on a basal diet failed to develop either the symptoms or the blood changes seen in the other groups. The bone marrow changes, too, were entirely dissimilar. Since the diet which produced the syndrome in animals was shown to contain vitamin B₁ and B₂, and the syndrome could not be produced by feeding diets lacking those vitamins, it would appear that a deficiency of any known factor of vitamin B was not etiological.

A digest prepared by incubating 12 Gm of vegex with 150 cc of gastric juice obtained from individual swine with achlorhydria and macrocytic anemia was fed daily to a patient with pernicious anemia at a definite hematological level for ten days. There was no reticulocyte response. Following this vegex and normal gastric juice of the swine was fed, and on the eighth day the reticulocytes rose to 28.2 per cent. An extract of the liver of achlorhydria swine was made and administered parenterally to a patient with pernicious anemia. There was no increase in the reticulocytes or blood elements. Following this the extract from the liver of a normal swine with normal gastric juice was given to the same patient, and

on the ninth day the reticulocytes rose to 21.2 per cent. This was followed by an increase in red cells and hemoglobin.

It appears, therefore, that the livers of swine which developed the achlorhydria, anemia, and mouth lesions did not contain the antianemic substance of liver which was present in the livers of normal swine.

Microcytic Anemia—The hogs that developed the microcytic anemia with hypochromia, which was never of the marked degree observed in experimental anemia resulting from the lack of the fundamental molecules, such as iron and copper, closely resembled the mild microcytosis observed early in the course of sprue and more rarely met in the course of that disease when a multiple deficiency is present.

Oral Mucous Membrane—Atrophic glossitis similar to that produced in dogs and seen in sprue, pellagra and pernicious anemia occurred in rare instances. However, localized ulcerated lesions of the lips, buccal and even laryngeal mucous membranes were striking in their frequency and extent. Miller and Rhoads²² assume that these lesions are similar to the aphthous stomatitis with ulceration, which is so marked a feature of tropical sprue. There was a definite loss of thickness with atrophy of the gastric mucous membrane in these hogs.

Miller and Rhoads state the lack of complete understanding of the mode of production of the symptom complex should not obscure the fact that the feeding of black tongue producing diet gives rise to symptoms in animals which not only simulate pellagra in man, but also, when studied under particular similar conditions, simulate sprue and pernicious anemia, from which one might infer that the three conditions in man and the experimental conditions have a nutritional defect that is similar and that the production of these conditions might be due to a lack of this substance. The experimental production of black tongue in dogs on a diet composed principally of corn meal but also containing casein, sugar, cotton seed oil, cod liver oil, and a salt mixture may be prevented or cured in its early stages by the administration of yeast or meat. There is a parallelism between vitamin B complex

and the factor preventing black tongue⁵³ Rhoads and Miller⁵⁴ produced chronic black tongue in dogs with anemia

Pellagra—Pellagra is described as a chronic noncontagious disease, presenting typical cutaneous lesions, symptoms referable to the gastro-intestinal tract and nervous and psychological disturbances Ludy⁵⁵ states that the cutaneous manifestations occur in the covered as well as the uncovered portion of the body, and that the malady also attacks the colored race Goldberger and Wheeler⁵⁶ state that it is possible to prevent the development of pellagra and cause the early symptoms to disappear by giving a diet rich in vitamin B₂ Mellanby⁵⁷ considers that vitamin B₂ deficiency is responsible for the skin lesions and vitamin A the cord lesions Savry⁵⁸ discounts the vitamin theory, attributes the cause to a toxin referred to as dioxyphenylalanine

Pellagra is very common in Egypt The peasants are notorious maize consumers, while the inhabitants of the large cities and towns are great bean and cheap liquor consumers McLester⁵⁹ feels that the avitaminosis theory is difficult of acceptance because it is impossible to relate the production of the disease in each instance to a dietary cause, and, second, because of certain epidemiologic characteristics Pellagra develops at times in people who are apparently well nourished and whose diet contains no gross fault He has seen cases in which a well-balanced diet rich in vitamin B complex, with an abundance of yeast, exerted no effect upon the fatal course of the disease In most deficiency diseases, notably in scurvy and polyneuritis of fowls, the correction of the dietary fault brings about prompt beneficial results The results with treatment of pellagra were considered to be less satisfactory From the epidemiological standpoint it must be pointed out that the disease appeared suddenly in the Alabama Insane Hospital in the first few years of the present century Pellagra occurred in epidemics from 1905 to 1929 in the insane hospitals of Alabama, Georgia and South Carolina Pellagra seems to spread from a definite focus both in individual cases

and epidemic form, whether the focus be a single house, a country or a state

The results of Goldberger's experiments on the eleven volunteer convicts given a grossly deficient diet are open to question. McLester feels that we can't rule out the possibility that the disease, although it may be due to a multiple food deficiency, may also be infectious in nature. This would explain its sudden appearance and rapid spread. It would also explain the fact that it is less fatal than when it first appeared. Spies⁶⁰ states that the majority of cases of pellagra observed in the northern part of the United States are associated with chronic alcoholism. The indulgence of alcohol at times prevents an adequate food intake, thus favoring the production of pellagra. Postalcoholic dermatitis and the skin lesions of pellagra appear identical. Six cases of true pellagra were studied and placed on a diet low in minerals and vitamins C, D and B₂. All had a history of low food intake and four the history of alcoholism. The diet used in the experiment was restricted as to mineral content and vitamins D, C and B₂ and Goldberger's pellagra producing diet. Five of the six patients improved strikingly on this so-called "pellagra producing diet". A high percentage of the cases with pellagra have achlorhydria, which usually disappears several months after recovery from the disease.

The blood picture has been variously reported as no anemia in certain numbers, microcytic anemia, and in a few cases macrocytic anemia, but Turner⁶¹ concluded that 56 per cent showed no appreciable anemia, 16 per cent slight, 12 per cent moderate, 12 per cent severe, and only 4 per cent extremely severe anemia. The anemia when present was of the hypochromic microcytic type. Spies⁶² states that about 60 per cent of the patients with severe pellagra have a definite anemia. One third of these are hypochromic microcytic, and 40 per cent have an anemia of the macrocytic hyperchromic type. The difference in the findings of Spies and Turner may be due to the fact that the cases seen by Spies were the severe type, while those seen by Turner were of the more mild variety.

Treatment—In addition to the dietary regime, good results have been reported with thyroid extract, 2 grains daily, and sodium thiosulphate intravenously Ruffan and Smith⁶³ report little or no improvement when liver extract No 343 was given intramuscularly in doses of 5 cc daily Spies⁶² reports good results in severe cases by the intravenous injection of 3 to 5 doses of liver extract of 20 cc each He emphasizes the point that in order for treatment to be effective the dose must be much larger than that used for cases of pernicious anemia Aqueous⁶³ liver extract—Valentine's E-29—was administered by mouth, with marked clinical improvement Two cc of E-29 is roughly equivalent in vitamin B potency to 200 mg of dried brewer's yeast Brewer's yeast, 15 Gm daily, has benefited many patients with disease Wheat germ in amounts ranging from 250 to 350 Gm daily was found to be efficacious by Spies⁶² The wheat germ is more readily tolerated by patients than is yeast Spies⁶² states that peripheral neuritis and central nervous system involvement occur in two thirds of the patients Liver extract parenterally administered has not been proved to have a direct effect upon the disturbances of the nervous system It does, however, heal the gastro-intestinal tract, and in so doing aids in the absorption of the necessary food substances capable of curing mental and neurologic phenomena Ventriculin produced characteristic remissions, and Spies observed that ventriculin prevented the signs of vitamin B₂ deficiency in rats Spies uses ventriculin in doses of 200 Gm daily, powdered yeast 75 to 100 Gm daily, and powdered liver extract 75 to 100 Gm daily Spies and Payne⁶¹ incubated the gastric juice of two patients with active pellagra with 200 Gm of beef muscle and fed this to two patients with pernicious anemia, and in each instance a characteristic hematopoietic response occurred This suggests the fact that although achlorhydria exists, the intrinsic factor is present There are many points of similarity between pellagra and pernicious anemia

Sprue—Sprue is a disease in which glossitis is present in varying degrees from a coated ulcerated tongue to the dark

red, raw beef tongue in the late stages. There are recurring attacks of diarrhea. The stools are large, light colored, frothy, and contain an excess of fat. Loss of weight and weakness are progressive. An anemia develops which may vary from the mild hypochromic microcytic type to the severe macrocytic hyperchromic, resembling pernicious anemia. Sprue is not found in all the tropical countries. It is common in Puerto Rico, but less common in Cuba and in Central and South American countries. Some of the tropical sections of China have no sprue, while in others it is common, although the natives exist on a diet that is essentially similar.

Harris⁶² states that the epidemiological studies suggest that it is an infectious disease. A similar statement, as we know, has been made for pellagra by McLester. Ashford⁶⁶ believes that the *Monilia psilosis* is the organism responsible for the production of the disease. It is found in the scrapings from the tongue in most of the cases of sprue. Some observers believe that Ashford is correct, while others feel that the *Monilia psilosis* is not pathogenic. Wood⁶⁷ found the organism constantly in the mouths of patients with pernicious anemia. That there is some pancreatic deficiency in the majority of patients with the disease seems to be supported by the observations of some clinicians. To support further the contention that we are dealing with an infection are the facts that the condition develops in more than one member of a family, and that persons living in houses in which patients have died with the condition develop it, and that the natives seem to develop some sort of an immunity to it.

As with pellagra, the excessive use of alcohol seems to predispose to sprue. The white man in the tropics often drinks excessively and is more prone to develop sprue than the natives. That many of the individuals who develop this disease live on a vitamin poor diet is well established. However, there are many sections of tropical countries in which the natives live on a poorly balanced diet, deficient in vitamins, and sprue is practically unknown.

In a typical case of sprue there is a chronic inflammatory

change in the entire alimentary tract The tongue is similar to that seen in pernicious anemia The liver is reduced in size There are changes in the gastric mucous membrane, usually an absence or greatly reduced free hydrochloric acid content, and Castle has shown that the intrinsic factor is lacking in large numbers of these patients The bone marrow shows changes similar to that seen in the typical pernicious anemia patient, that is a megaloblastic hyperplastic bone marrow Like pernicious anemia, some of the patients with sprue develop evidence of cord change

Treatment—In the treatment of the condition a diet high in protein, rich in vitamins B and C has been recommended as the cure for the majority of the cases Strawberries—from a pint to a quart a day—bananas—from six to twenty-four—have been used successfully in the treatment of this condition Two to 4 quarts of milk and an all-meat diet also have their champions Blood transfusion and vaccine therapy, as suggested by Ashford, have been recommended As a result of the work of Minot, Castle, Sturgis, and others, whole liver, liver extract, both aqueous and powdered, ventriculin and liver extract parenterally have been effective in the treatment of this disease, bringing about adequate reticulocyte response and red cell, hemoglobin increases and alleviation of symptoms Similar results have been obtained by Castle with the use of vegex incubated with normal gastric juice Marmite and alcoholic extract of brewer's yeast have been used successfully in some patients with sprue

Dibothriocephalus Latus Anemia—In Finland today 750,000 are infested with the fish tapeworm, but only 5000 or 10,000 are known to have a definite anemia⁶⁸ Achlorhydria is present in 84 per cent of the cases, and following adequate treatment there is a return of the hydrochloric acid in one third Some of the patients die from the anemia, despite the removal of the worm Some are cured of the anemia and the parasite, but at a later date harbor it again without developing an anemia Glossitis occurs, but it is not as common nor as marked as that which is seen in pernicious anemia One finds

all grades of anemia, some very slight, some very severe. In the marked cases there is usually an increase in cell diameter. The bone marrow is hyperplastic, with an increase in megaloblasts and erythroblasts, although the change is not as marked as that seen in true pernicious anemia. Evidences of definite cord change have been noted in a few cases, but the majority of the reports are inconclusive. Numbness and tingling are commonly associated with the severe forms of the anemia. The stomach mucous membrane usually does not show as marked change as is seen in true pernicious anemia cases. If the patients are treated with liver or liver extract, a response occurs similar to that seen in the pernicious anemia patient who is parasite free. Birkeland⁵⁸ states that many of the patients show a dramatic response of reticulocytes and red cells when the parasite has been removed from the intestinal tract by adequate treatment.

That there is a causal relationship between the presence of the intestinal parasite and the development of the disease is rather uncertain. The fact that the patient improves when given material effective in true pernicious anemia, even though the parasite is still in the intestinal tract, is against such a relationship. However, the point that the patient shows a good reticulocyte and red cell response in some cases after removal of the parasite suggests that the two conditions may be related. It may be that the presence of the parasite in some manner conditions the gastro-intestinal tract so that the factors necessary for the stimulation of hematopoietic responses are not utilized. In favor of this conception is the fact that one third of the patients with achlorhydria experience a normal gastric function after adequate treatment. This is comparable to the change in the gastric secretion which is seen in pregnancy.

Anemia of Pregnancy—Strauss and Castle⁵⁹ state that the hypochromic anemia of pregnancy is analogous to the idiopathic hypochromic anemia in the nonpregnant. The etiologic mechanisms are similar, direct dietary deficiency and indirect dietary deficiency conditioned by a gastric defect. Iron therapy is efficacious in the treatment of both conditions.

The macrocytic hyperchromic or pernicious anemia of pregnancy presents many features in common with the typical pernicious anemia. In the pernicious anemia of pregnancy free hydrochloric acid is usually absent, and in some cases the intrinsic factor is either absent or else greatly reduced in amount. Very often in these cases there is a return after delivery of both hydrochloric acid and the intrinsic factor. The administration of liver extract, ventriculin by mouth and liver extract intramuscularly brings about a reticulocyte rise which is followed by an increase in red cells and hemoglobin. Data on the use of autolyzed yeast products or brewer's yeast or wheat embryo extract is not at hand, although, as pointed out before, marmite fed to pregnant patients with tropical macrocytic anemia brings about desired results. It may be that similar results might be obtained in the type of anemia under discussion.

Tropical Macrocytic Anemia—Tropical macrocytic anemia occurs frequently in association with pregnancy, or it may complicate or be complicated by malaria, hookworm or sprue. No free hydrochloric acid is present. A hyperchromic anemia of considerable degree develops. Six hundred Gm of fresh liver daily bring about an adequate response of reticulocytes and red cells. Marmite—1 drachm four times a day—produces a result similar to that obtained by liver.

Idiopathic Steatorrhea—Celiac disease in adults most often shows a hypochromic microcytic anemia with pallor and edema. In some patients, however, no anemia is present. Vaughan⁷¹ reports 20 cases of hypochromic microcytic anemia. The anemia may be hypochromic at first, but later hyperchromic. Diarrhea is a common symptom. The stools contain a great deal of fat, 45 to 50 per cent of which is neutral fat, and 25 to 30 per cent fatty acids. Free hydrochloric acid is present in most cases, but is absent in a few. Sore tongue is a frequent symptom. The bilirubin is normal or reduced. Liver extract by mouth produces an adequate reticulocyte response, but administration of marmite also brings about similar results.

Macrocytic Anemia in Association with Mechanical Defects in the Gastrointestinal Tract—*Gastrojejunal Colic Fistula*—Gastrojejunal colic fistula usually originates from cancer of the stomach or colon or follows the operation of gastro-enterostomy.¹² Diarrhea is often the first and most constant manifestation. The stools are yellow and acid in reaction due to hydrochloric acid and fatty acids. The anemia is usually of the macrocytic type. Hyperacidity is very often present. The patients do well as far as the anemia is concerned on liver or stomach extract. Castle, Townsend and Heath¹³ found the gastric juice of a case of macrocytic anemia with multiple anastomoses of the small intestine contained large amounts of hydrochloric acid, pepsin and rennin, but was deficient in the intrinsic factor. The anemia responded well to liver extract. The blood bilirubin is normal or low, as is the blood calcium.

Multiple Intestinal Anastomosis and Macrocytic Anemia—Little and Zerfas¹⁴ report a case of a boy who had been operated upon for acute gangrenous appendicitis. Acute small bowel obstruction developed. This was relieved by operation. A third and fourth operation were performed in the two following years. The boy showed nutritional disturbances, abdominal pain, and diarrhea. Eight years after the first operation the anemia became prominent and progressed rapidly. An operation was performed, which relieved the symptoms and gave normal bowel movements without diarrhea. The patient did not take the suggested medication and was readmitted with a blood count of 2,020,000 and hemoglobin 50 per cent. Free hydrochloric acid was present in the stomach in normal amount. The anemia was of the macrocytic hyperchromic type. Liver extract was administered and there was a reticulocyte response of 27 per cent on the tenth day. As long as the liver extract was given in adequate amount the symptoms and the blood count were controlled.

Anemia after Gastrectomy and Gastro-enterotomy—The incidence of anemia in gastrectomy depends particularly on the extent of the operation and also upon the rate of emptying.¹⁵ The more quickly the stomach empties, the more likely

is an anemia to develop Atrophic tongue has been noted in past years after gastro-enterostomy and also after gastrectomy Achlorhydria is present Some of the patients show the extreme nail changes, that is spading and spooning, and some only brittleness Iron and acid administered to this type of patient brings about a good result Bloomfield believes that the vast majority of cases in which gastrectomy is performed do not develop an anemia of the addisonian type The operative mortality in total gastrectomy is high Finney and Rienhoff⁷⁶ report a mortality of 53.8 per cent Only two of the patients lived longer than two and a half years Most of them succumbed to an early occurrence of the carcinoma The average interval between the operation and the development of pernicious anemia was six and one-tenth years, the shortest one and one-half, and the longest fourteen Ungley⁷⁷ reports a case in which pernicious anemia developed five months after complete gastrectomy The color index was high and there was an increase in the average diameter of the cells Treatment with cooked liver was followed by a great clinical improvement and increase in weight

Alcoholic Neuritis —Pellagra frequently is seen to occur in association with rectal stricture, gastro-enterostomy, intestinal stenosis, gastric carcinoma, pyloric obstruction, and other lesions of the gastro-intestinal tract It has been pointed out by Strauss that both the alcoholic polyneuritis and that seen in association with the pernicious vomiting of pregnancy are the result of the conditioning of the gastro-intestinal tract and not due to a neurotoxic factor Strauss showed that chronic alcoholics who were permitted to take from a pint to a quart of whisky daily could be relieved of the polyneuritis by the administration of adequate amounts of vitamin B Spies and Blankenhorn (personal communication) found that the neuritis of the chronic alcoholic and the pellagrin could be relieved when the individual was fed adequate amounts of vitamin B or ingested a sufficient well-balanced diet

Beriberi —Beriberi is a disease due in most instances to excessive consumption of polished white rice It occurs chiefly

in the tropical and subtropical countries. It is characterized by multiple peripheral neuritis, cardiac weakness, respiratory irregularities, edema, fever and gastro-intestinal disorders. The etiology of the disease has been said to be due to bacterial invasion, to the presence of malarial plasmodium, to exposure, to cold and dampness, to the use of alcohol and to malnutrition. Years ago it was shown that when polished rice was fed to fowls a polyneuritis developed. A series of experiments on laborers in the Malay Peninsula showed that the disease could be prevented by feeding parboiled rice, and would occur if the same individuals were fed polished rice. The essential substance which is removed has been found to be the antineuritic vitamin B.

Most writers conclude that the vitamin deficiency is not the only factor in the production of the disease. Beriberi has been noted to occur in association with celiac disease, ulcerative colitis, and in certain cases of intestinal anastomosis and stenosis. The essential pathological change is parenchymatous degeneration in the nerve filaments of the peripheral nerves. Muscular atrophy takes place. Gastritis and enteritis with hemorrhage have been reported. The treatment requires the elimination of polished rice and the addition of a well balanced diet, the avoidance of exposure, dissipation and infectious disease. Strangely Wrigley¹⁸ has been able to bring about complete cure in incipient cases by 5 drops of iodine daily. An explanation of this is not evident.

NUTRITIONAL ANEMIAS OF MICROCYTIC TYPES

Idiopathic Hypochromic Anemia (Simple Achlorhydric Anemia)—Attention was first drawn to this condition in 1913 by Faber¹⁹. The disease is very much more common in women. In one series 49 of the 50 cases were females, in another only 4 of 55 cases were males. It occurs most often between the ages of thirty five and fifty. The duration of the anemia is often five or ten years, and gastro-intestinal symptoms may be present for even a longer time. fissures and painful cracks at the angles of the mouth and atrophic glos-

sitis are found frequently The patient may not complain of the soreness of the tongue, but from its appearance one would imagine that it should be sore In the absence of redness, the glazed tongue is a valuable diagnostic feature Very often the nails, which are unusually brittle, split longitudinally They are flat or spoon shaped, or spadelike in some patients The spleen is enlarged when the anemia is marked Under treatment this tends to reduce in size Disturbances of menstruation are common features It is not unusual to find the hemoglobin 40 per cent and red cells 4,000,000, giving a low color index Most of the patients show a microcytosis, although Wills⁸⁰ reports a few cases in which there was a macrocytosis The white cell count varies between 3000 and 7500 Serum bilirubin is always low The gastric juice is absent There is an increased amount of mucus and the stomach empties rapidly Pepsin is present, but reduced in amount

The disease is not materially affected by the administration of liver or stomach extract Iron in the proper medium and properly absorbed, however, brings about satisfactory hematopoietic response From many of the patients one can obtain the history that they have not eaten meat or green vegetables for years Milk, rice and potatoes are all poor in iron Red meat contains 17-20 mg of iron per 100 Gm of dry substance Wheat flour contains only 1.6 mg Mettier and Minot⁸¹ showed that iron is absorbed best in an acid medium

Wintrobe and Beebe⁸² in their summary of the findings in idiopathic hypochromic anemia state that the disease is an anemia of unknown etiology, occurring especially, but not exclusively, in women in the third to fifth decades of life It is characterized by an insidious onset, long duration, symptoms common to anemia in general, and, in addition, glossitis, stomatitis, dysphagia, paresthesia, often splenomegaly and nail changes Achlorhydria is present in the majority of cases There is ready response to iron, but a tendency to relapse is a common feature They suggest that the fundamental disturbances may be defective gastric secretion with faulty

utilization or synthesis of the material from the diet which is necessary for hemoglobin formation. The requirements of menstruation and rapid pregnancy may explain the preponderance of the condition in the female.

Plummer Vinson's Syndrome—Vinson⁸³ first described this condition. It is similar to the idiopathic hypochromic anemia. Dysphagia is the added symptom. Most of the patients, but not all, show an absence of free hydrochloric acid. The laryngologists are inclined to the belief that dysphagia is the primary factor. As a result of this dysphagia the individual does not take anything but liquid food, which usually resolves itself into milk and tea, etc. The anemia responds well to iron given in an acid medium. However, the addition of vitamin B complex products, and, of course, treatment of the lesion causing the dysphagia add much to the permanency of the cure. It has been stated that there is a better gastric secretion in these patients when their blood count is improved.⁸⁴ However, Davy states that the patients that he examined with this point in mind showed no improvement.

Suzman⁸⁵ believes that the so-called "Plummer-Vinson's syndrome" should not be classed as a separate clinical entity, but simply one that may arise in idiopathic hypochromic anemia. He cites cases in which the anemia preceded the difficulty in swallowing by as long as two years. Cameron⁸⁶ noted that in 15 patients dysphagia preceded the pallor, and that in 5 the pallor preceded the dysphagia by a considerable interval. This is not in agreement with the thought that the difficulty in swallowing interferes with the proper food and iron intake necessary to sustain a normal hemoglobin level. Suzman further points out that esophageal lesions and consequent dysphagia are probably the result of an extension to the pharyngeal esophageal region of the lesions of the mouth and tongue, these lesions are present for a considerable time before the difficulty in swallowing is noticed. He states further that the occurrence of webs and of raised mucous membrane

obstructing the esophagus may be a factor in the production of this symptom

Patek and Minot⁸⁷ state that the administration of bile pigment alone to patients with chronic hypochromic anemia causes an increase of hemoglobin of about 7 per cent in ten days, without reticulocyte response. After a reticulocyte response occurred to a suboptimal dose of iron, bile pigment was fed with the same dose of iron, and a second reticulocyte response occurred which was often greater than the first. Bile pigment, therefore, in form unknown may facilitate either iron absorption or utilization. This suggests that in certain patients with hypochromic anemia there may be a deficiency of a useful material that is contained in bile pigment in addition to iron deficiency.

Idiopathic Hypochromic Anemia and Macrocytic Hyperchromic Anemia—Wintrobe and Beebe⁸⁸ observed a patient for twelve years who suffered from a chronic anemia associated with glossitis, achlorhydria, splenomegaly and nail changes. The symptoms appeared during her first pregnancy. She was observed in the sixth month of her seventh pregnancy. The anemia was microcytic hypochromic, but failed to respond to adequate vitamin B₁₂ and iron therapy. It was found that the anemia which was marked had become macrocytic and on an intensive liver therapy the reticulocytes rose to 17 per cent, followed by rapid degeneration of red cells. The mean corpuscular volume is at the present time within normal limits, but a moderate anemia still exists which does not respond to iron and liver therapy.

Comment—*Intrinsic Factor*—One may conclude from the study of the present-day literature that there seems to be three factors related to the development of the condition pernicious anemia. Regarding the intrinsic factor, which may be termed factor I, in spite of the work of Barnett, who found the intrinsic factor present seemingly in adequate amounts in some patients with pernicious anemia, and who was unable to bring about a reticulocyte response in a patient with pernicious anemia to whom the normal gastric juice, beef muscle

mixture, was given, and in spite of the fact that Bloomfield has studied patients with achlorhydria and absent or greatly diminished amounts of the intrinsic factor, who failed to develop evidence of pernicious anemia. There is a large number of data supporting Castle's original conclusion regarding the intrinsic factor. Which theorem we feel should be accepted, at least at the present

As to the other conditions, which in some respect are similar to pernicious anemia, that is pellagra, sprue, pernicious anemia of pregnancy, tropical macrocytic anemia, Dibothriocephalus latus anemia, the intrinsic factor has been found to be present in some, namely pellagra, tropical macrocytic anemia, and variably absent, reduced or present in seemingly adequate amounts in the other conditions

Such findings might detract from the importance of the intrinsic factor, but in most of these conditions we find that there is some conditioning factor in the gastro-intestinal tract which prevents the proper utilization of the antianemic factor. Further evidence of this is to be found in the anemia occurring in such conditions as multiple intestinal anastomosis, intestinal stenosis, gastrocolic fistula and gastrectomy, in which, with the exception of gastrectomy and gastric polyposis, there usually are sufficient intrinsic factors, but because of the condition of other portions of the intestinal tract, the material formed is unable to be utilized in sufficient quantity to keep the blood at a reasonable hematologic level

Extrinsic Factor—The nature of the extrinsic factor has received a great deal of consideration from the experimental standpoint, chiefly as to whether or not it is vitamin B₁ or B₂. The two autolyzed yeast preparations, vegex (American) and marmite (British), have been used extensively in the conditions under consideration. Vegex alone has not produced adequate reticulocyte response when administered to patients with pernicious anemia. Marmite, however, as Ungley pointed out, did bring about a satisfactory response in 1 patient and a fairly good response in another. In subsequent trials in other patients he was unable to duplicate the results. Marmite and

ministered to patients with tropical macrocytic anemia produces adequate reticulocyte response and other evidences of recovery. Vegex, when incubated with gastric juice and administered to pernicious or sprue patients, brings about a satisfactory response. Spies has pointed out that material given to patients with pellagra must be administered in much larger amounts than is necessary for the pernicious anemia patient. It may be that the dose of vegex, which as a rule has been much less than the dose of marmite, explains the lack of effect when used alone in some of these patients.

With regard to the question of whether this extrinsic factor is vitamin B₁ or B₂, Miller and Rhoads feel that there is a parallelism between vitamin B complex and the factor preventing black tongue in dogs. They conclude, however, in their work with swine, that the diet which produced the pernicious anemia-like syndrome was shown to contain vitamin B₁ and B₂, and in the animals in which there was a lack of these vitamins in the diet no pernicious anemia-like syndrome was produced. Furthermore, egg white, and egg white incubated with gastric juice, has been fed to patients with pernicious anemia without response. The vitamin B content of marmite has been reduced to a minimum or destroyed entirely and yet when incubated with normal gastric juice it was able to bring about adequate responses in pernicious anemia patients. On the other hand, we have evidence that the administration of large amounts of wheat embryo extract, brewer's yeast, and liver extracts containing vitamin B complex have brought about adequate responses in patients with pellagra, sprue, tropical macrocytic anemia, and the pernicious anemia of pregnancy.

These points emphasize the fact that we know as little about the nature of the vitamin B complex as we do of the nature of the extrinsic factor. The answer may lie in the point that, when vitamin B complex is ingested, it stimulates an outpouring of a sufficient amount of intrinsic factor which is not present under normal conditions in that patient or which has not been stimulated by histamine injection, and that this

intrinsic factor interacts with the vitamin B complex to produce the antianemic factor, just as occurs outside the body when the vitamin B complex is incubated with normal gastric juice

Antianemic Factor or Liver Active Principle—As a result of the interaction between the intrinsic and extrinsic factors the liver active principle is formed, which is absorbed and stored in the liver. As has been pointed out, certain livers are unable to store this material and an anemia develops. Miller and Rhoads demonstrated experimentally the fact that the liver of inadequately treated hog when injected into the pernicious anemia patient did not bring about suitable response. The nature of this substance has not as yet been determined.

With regard to the action of addisin and the injection of liver extract into the bone marrow cavity, further experimentation may throw light upon the results obtained, but in all probability the answer will be found in the concepts already set forth.

This study emphasizes the importance of nutritional deficiency factors in the production of anemia. The deficiencies in the stomach itself, the lack of suitable quantity of extrinsic factor in the diet or a lack of iron and copper in the diet, the fact that even with adequate intake and normal gastric conditions, the other portions of the gastro-intestinal tract may be so conditioned that the materials cannot be utilized, and finally that with all portions of the gastro-intestinal tract acting normally and with a normal intake of extrinsic factor and of minerals, the liver may not be able to store the materials that are adequately absorbed.

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THE NEUROLOGICAL MANIFESTATIONS OF PERNICIOUS ANEMIA AND THEIR TREATMENT

ABOUT 80 per cent of the cases of pernicious anemia present a symptomatology, the etiology of which can be ascribed to changes in the nervous system. However, in only about 15 to 20 per cent are the manifestations dependent upon subacute combined degeneration of the spinal cord. Boyd describes the pathologic changes that take place in the cord in pernicious anemia as follows. The cord is swollen first in the posterior columns, then the lateral columns, and finally the anterior columns are involved. The lesions coalesce and form a ring of degenerated tissue around the gray matter. This is a characteristic lesion. The process usually begins in the lower dorsal region and spreads up and down. The distribution is often spotty. Microscopically there is a breaking up and degeneration of the medullary sheaths, followed by disappearance of the axis-cylinder. There is a complete absence of neuroglial proliferation. Degenerative changes take place in the peripheral nerves. A few cases have been described in which lesions have been found in the brain. An increase of glia fibers such as one sees in multiple sclerosis does not occur. The posterior roots are not involved. The following symptoms may be ascribed to lesions of the nervous system, numbness and tingling, absent or diminished vibratory sense, weakness, ataxia, astereognosis, positive Romberg, loss of muscle sense, spasticity, increased reflexes, diminished reflexes, positive extensor response (Babinski), disturbed cutaneous sensibility (paresthesias), sphincter disturbances, psychic disturbance, trophic ulcer, disturbances of memory and vision.

In the past pernicious anemia has been divided into those cases which develop no evidence of neurologic change, those which had evidence of peripheral nerve involvement, those with

cord changes and peripheral nerve involvement, developing late in the disease, those with cord and peripheral nerve involvement that developed early in the disease, and those with cord and peripheral nerve involvement that were present before the anemia was evident. The older pathologists stated that every case of pernicious anemia that was necropsied showed cord change, even though no demonstrable symptoms or signs were present during life. One questions the statement that there are cases of pernicious anemia with symptoms and signs of cord change which are present before the anemia develops.

Before the advent of the use of liver and allied substances in the treatment of pernicious anemia, the presence of the evidence of cord change was viewed with grave concern, and even after Minot and Murphy brought out the value of liver many observers^{1 2 3 4} noted slight, if any, improvement in the signs and symptoms. These poor results probably were due to the fact that the liver was not administered or absorbed in sufficient quantities to affect the patient favorably.

Ungley and Suzman⁵ reported 17 patients improved, 8 unimproved, and 5 deaths. Richardson⁶ found improvement when the symptoms were tabetic in type, but no improvement when spasticity was a marked symptom. Baker, Bordley, and Longcope⁷ report improvement in 31 per cent of the signs and symptoms of nervous system involvement in cases treated for less than six months, 55 per cent in cases treated for more than six months, and 59 per cent in patients with advanced subacute combined degeneration who were under treatment for more than ten months. The noticeable improvements were in those signs and symptoms referable to disturbances of cutaneous and muscular sensibility and to flaccid paresis.

Suzman⁸ in a study of 113 patients with nervous system involvement found that improvement occurred in 55 of the 100 cases in which liver treatment was used, 19 patients failed to improve and 26 died. Sixty-one patients, however, who had no treatment with liver died. The most important cause of death was septic complications—urinary infection, bed sores, etc. He reports that paresthesias disappeared in 11 per cent, almost

negligible in 18 per cent and improved in 67 per cent. Other dysesthesias, as rough skin, cramps, girdle sensations, tended to improve or disappeared under treatment. Joint sensibility became normal in 57 per cent of the cases in which it was present. Coordination of the lower extremities became normal in 20 per cent, 64 per cent showed slight degrees of impairment, in 16 per cent, although the function was grossly defective, there was still some improvement. Vibratory sense showed no change in 93 per cent, and in only 4 cases did this form of sensation return. Astereognosis disappeared completely in 3. Vision returned to normal in 5. Memory improved remarkably in 3. Psychoses disappeared in 2 of the 3 cases in which they had been present. As to the deep reflexes, the only significant change was the occasional return of hyperactive reflexes to degrees of activity within normal limits. This was accompanied by a gradual disappearance of ankle clonus and a diminution of spasticity. The plantar reflexes in some cases showed a return to normal or nearly normal response. Significant alterations in the nature of the plantar reflexes occurred in 10 of the 36 improved patients. In 8 of these the reflexes returned to normal in one or both limbs. Sphincter disturbances cleared up completely in all cases in which they occurred. Difficulty in walking—of the 55 cases 25 returned to normal, 17 showed slight unsteadiness, 4 used a cane, 8 needed crutches, and 1 was bedridden.

Goldhamer, Bethell, Isaacs, and Sturgis⁹ report that 364 or 89.2 per cent of 408 patients with pernicious anemia showed nervous system involvement. Of this group 43.2 per cent had symptoms of cord change at the onset of the disease, 46 per cent developed the changes at some period during the illness. Cerebral symptoms occurred in 64 per cent. Of 126 adequately treated patients in the male group with demonstrable cord lesions, 61 had posterior horn degeneration, 1 had lateral tract degeneration, and 64 had no demonstrable cord lesions. Of the 11 patients with no demonstrable cord lesions, cord involvement developed in 5. Of the patients with posterior horn degeneration 15

showed improvement in symptoms and 4 improvement in signs. In 3 symptoms became more severe and in 6 the physical signs progressed. Of the 53 patients with combined degeneration symptoms were improved in 23, unchanged in 23, and accentuated in 25. The signs were not improved in any, and progressed in 5.

The Principles of Treatment.—Irrespective of the form of therapy used, it must be given in adequate amounts, produce adequate reticulocyte and red cell response, be taken at intervals sufficient to keep the blood count at normal or above normal as long as the individual lives. Ground fresh uncooked liver administered in orange juice, or ginger ale, or tomato juice in amounts of 480 Gm daily is suggested. If this is utilized and absorbed, it is more than sufficient to keep the blood at a suitable level. However, many of the patients rebel at eating that much fresh liver or even cooked liver daily and accordingly fail to receive adequate amounts of the necessary substance, which results in a fall in the blood count and a return of the symptoms referable to the nervous system change.

Aqueous liver extract E-29 (Valentine), 3 to 6 ounces daily, has brought about favorable results in certain patients. Ventriculin, 30 to 90 Gm daily, has also been used successfully, although Sturgis is of the opinion that it may not be as effective as whole liver or parenteral liver in the treatment of this condition. Strauss *et al*¹⁰ believe that parenteral liver extract administered in adequate dosage at suitable intervals prevents the occurrence of neurologic phenomena and brings about marked improvement in those patients with neurologic phenomena who present themselves for treatment. On the basis that the changes in the cord and peripheral nerves may be similar to those seen in conditions which we have discussed previously, such as sprue, pellagra, and beriberi, products containing large amounts of the vitamin B complexes have been suggested. Such substances as vegex, marmite, wheat germ extract have been used, but there is no evidence at hand to support the contention that they are of specific value. In fact, Ungley¹¹ states that the neurological complications of perni

cious anemia do not respond to wheat germ, even in large doses. The mechanism responsible for the development of this condition resembles that which gives rise to pernicious anemia, and each is the result of nutritional deficiency conditioned by a gastric defect. The two conditions do not necessarily arise from a lack of the same substance. It is suggested that in the brain and in the liver there is a substance beneficial to the neurological phenomena which is distinct from that influencing blood regeneration. Investigation of the dietary history of cases of pernicious anemia with cord involvement fails to bring to light any difference in the intrinsic and extrinsic factor, but of importance is the fact, according to Ungley, that there is a high incidence of subacute combined degeneration in pernicious anemia associated with the extensive gastric lesions, such as polyposis. This suggests that the neurological condition may be due to a gastric secretory deficiency quantitatively greater or different from that occurring in cases of pernicious anemia without nervous involvement. Certainly they are not indicated in patients in whom no neurologic phenomena have developed. If the signs and symptoms are present, however, it may be wiser to use some of these materials in adequate dosage until it has been shown that the deficiency of some substance in the vitamin B complex has no relation to the development of these phenomena.

Fever therapy has been used successfully in cases of multiple sclerosis. It has been tried in patients with pernicious anemia and subacute combined degeneration of the cord. The results of this with other therapy are given in the two following cases.

Case I.—A. M., aged forty seven, admitted to Jefferson Hospital December 1931.

Chief Complaint.—Nervousness tingling in the hands and feet, staggering gait, inability to locate position of feet.

Family History.—Negative.

Personal History.—With the exception of a few childhood diseases, the patient has always been well. Her appetite has always been excellent but taking of food in recent years has been followed by excessive gas formation and belching. As far as the patient can tell, the diet has been adequate and

sufficiently diversified The bowels are constipated Pregnancy has never occurred No operations or serious injuries Dental caries and root abscesses have been present in the last few years

Present Illness—In 1928 tingling and hyperesthesia of the feet began There was progressive weakness of the legs Gradually the patient lost the sense of her feet, but could walk fairly steady if she fixed her eyes on her feet Gradually her gait was unsteady and irregular no matter what she did She stated she had a stamping gait—came down on her heels She complained of difficulty in starting urination and at other times difficulty in controlling the bladder when full On her entry into the hospital she was bedridden

Physical Examination—Her skin was yellowish, with pallor of the mucous membranes Mouth infection was evident Heart and lungs were clear throughout The liver and spleen were not palpable

Cord changes Romberg markedly positive Gait atactic spastic Face and eyes negative

Upper extremities Grip good Deep reflexes markedly increased Ataxia present Numbness and burning of the fingers Inability to pick up small objects, such as a needle Astereognosis Abdominal reflexes diminished and unequal

Lower extremities Spasticity present Heat and pain sense preserved Muscle sense lost Vibratory sense lost Knee jerks greatly increased Bilateral Babinski and bilateral Chaddock present

Eyes Fundus pale Otherwise no change of importance

Laboratory Studies—December 2nd Hemoglobin 32 per cent, red blood cells 1,060,000, white blood cells 3500, color index 1.12, polymorphonuclears 36 per cent, lymphocytes 61 per cent, metamyelocytes 1 per cent, eosinophils 2 per cent, reticulocytes 0.2 of 1 per cent, platelets 160,000, volume index 1.19, clotting time four minutes, bleeding time three and one-half minutes, icterus index 15, van den Bergh indirect positive 1.19 mg, Wassermann and Kahn tests negative

Spinal fluid No increased pressure Less than 1 cell per cubic millimeter Sugar 48

Gastric analysis Showed no free hydrochloric acid present with a test meal and after histamine injection

Urine Specific gravity varied from 1.007 to 1.020, faint trace albumin, 50 to 74 pus cells, no casts seen

Blood pressure Varied between 80/60 and 120/80

Temperature 98° to 100° F

Pulse 100 to 120

Respirations 23 to 24

Diagnosis—Subacute combined degenerative spinal cord lesion, associated with pernicious anemia

Treatment—Liver extract was administered by mouth and fresh ground uncooked liver in orange juice in the amount of 1 pound a day, in addition to a well-balanced diet

Reticulocyte response

	Per cent
December 2nd	0.2 of 1
" 3rd	0.1 of 1
" 4th	0.3 of 1
" 5th	1
" 6th	3
" 7th	3½
" 8th	12
" 9th	24
" 10th	16
" 11th	8
" 12th	2

Blood counts

Date	Hemoglobin	Red Blood Corpuscles	White Blood Corpuscles
December 4th	34	1 110,000	3000
" 6th	35	1,200,000	3100
" 8th	35	1,320,000	3600
" 10th	38	1 400,000	3300
" 12th	40	1 480,000	3500
" 14th	45	1 100,000	4000
" 20th	50	2,620,000	4200
" 30th	60	3 160,000	5600
January 5th	72	3,810,000	6800
" 15th	80	4,200,000	8400

Polymorphonuclears 66 per cent lymphocytes 28 per cent eosinophils 2 per cent monocytes 6 per cent, platelets 228,000 volume index 1.01 icterus index 8 quantitative van den Bergh 0.063 Cells are normal in size and shape

Comment—The patient had improved in general physical condition put on weight, and, although she was unable to walk without assistance on either side the numbness and tingling was less and she was encouraged. Body massage and salt baths were started at this time. The improvement although slow was continuous. In June 1932 it was decided to give her fever therapy and diathermy.

At the time of her second admission the hemoglobin was 83 per cent, red blood cells 4,610,000 white blood cells 7600. Three diathermy treatments were given with good response as far as temperature rise was concerned. These treatments were discontinued because of some defect in the apparatus.

November 23th she was admitted again at which time her hemoglobin was 80 per cent, red blood cells 4,090,000, white blood cells 6100. She received 6 diathermy treatments and noticed marked improvement when she left the hospital.

Since that time she has been taking the ground liver in addition to liver extract or stomach extract by mouth. Veget or Harris's yeast vitamin in addition to a well-balanced diet have been taken regularly. In 1933 for six

days Lederle's liver extract (3 cc) was injected daily, and following this twice a week for a month, and then once a week

A successful attempt has been made to keep the blood count at a high normal, and during the course of the last two years, with one or two exceptions, the blood count has ranged about 85 per cent hemoglobin and 4,500,000 red blood cells. She is able to walk, can get out of a chair without assistance, feels her feet, has no numbness or tingling, is able to sew, do fine needle work and knit, and is steadily improving

She is able to walk without a cane, but carries one to give her confidence. The deep reflexes of the upper and lower extremities are not as active as formerly, but still hyperactive. The Babinski and Chaddock are still positive. Liver extract is given parenterally 3 cc weekly

Case II—A E, aged thirty-eight. The patient walked into the laboratory with some difficulty on October 6th, giving the following history

Chief Complaint—Generalized weakness and numbness of the extremities, inability to walk properly

Family History—Essentially negative

Personal History—The patient has never been ill except with some childhood diseases. His diet was well balanced and seemed sufficient. At the age of twenty-three, over a period of two years, he had severe attacks of epistaxis once monthly. Since that time to the present there have been no recurrences.

Present Illness—A year ago the patient noticed a numbness in the plantar surface of the toes. As he stood a great deal at work he thought it was due to that and disregarded it. About the same time he had several attacks of vertigo associated with vomiting. Toward the end of August, 1934, he began to experience the feeling of generalized weakness. At this time an anemia was discovered and he was given liver extract by mouth. There seemed to be less weakness and he was not as pale as formerly. The first week in September a numbness of the hands occurred and he began to notice peculiarity in his gait, which he described as "walking like a drunken man." In October his bowels began to move frequently, although he had no urinary symptoms. On October 6th his hemoglobin was 81 per cent, red blood cells 3,650,000, color index 1.1, white blood cells 7500, volume index 1.28, macrocytosis was present. The patient was able to walk out of the laboratory and returned to the hospital October 8th. At this time he had to be carried in on a stretcher as he could not stand up. Changes occurred so rapidly that in two days there was a marked change from ability to walk without aid, although unsteadily, to a complete loss of walking function.

Physical Examination—The physical examination of the head and neck was negative. The eyes showed no abnormality. The heart was of normal size. The lungs were clear with the exception of the right base, at which point there was an impairment of percussion extending almost to the angle of the scapula, diminished breath sounds and a few fine râles.

The neurological examination made by Dr M A Burns is as follows

"The patient is unable to walk or stand. The pupils are equal, regular, and react sluggishly to light. There is no evidence of nystagmus or ocular palsy.

"Upper extremities Marked ataxia in finger to finger test. Deep reflexes are lost The upper abdominal reflexes are present, lower abdominal absent Cremasteric reflexes are absent

"Lower extremities There is marked ataxia in the heel to-knee test, more marked on the right side. Patellar reflexes are lost. Muscle sense lost Babin ski and Chaddock signs are negative There is no ankle clonus There is evidence of posterior column defect The lateral tracts of the cord are not involved at this time

The eyegrounds examination by Dr Charles Heed is as follows

"The examination of the eyegrounds shows no gross lesions, no neuritis or atrophy although the disks are rather pale and the general color of the fundus is pale"

The gastric analysis showed no free hydrochloric acid after histamine stimulation

The spinal fluid examination showed no increased pressure normal amount of globulin and sugar the cells are 2 per cubic millimeter

Fluoroscopic examination of the chest showed a distinct limitation of the movement of the diaphragm on the right side

As soon as the patient arrived in the hospital that is October 8th he was placed upon a pound of fresh liver daily given in orange juice and from 80 to 120 Gm of vegex daily in addition to a well balanced diet. In spite of this active treatment the symptoms and signs of nervous system damage increased rapidly so that there was extreme ataxia of the upper extremities, loss of grip the patient was unable to sit up in bed and the following day was unable to turn in bed The lower abdominal reflexes which had been present, disappeared. A positive Babinski on the right side was noted

On the 9th of October 3 cc of Lederle's liver extract was given daily Because of the progression of the signs and symptoms and the dissatisfaction of the patient and his friends, on the 21st of October it was decided to give him a series of so-called "fever therapy" treatments These were administered by Dr William Schmidt and were given daily for ten treatments A temperature rise to 104 F was attained at each treatment after the first. The other forms of treatment were continued October 24th he did not complain of as much weakness, was able to move about more freely October 27th the patient felt much stronger but did not attempt to do anything with his arms or legs November 1st the patient had improved considerably in strength in both arms and legs He was able to recognize some objects placed in his hands The numbness in the arms and legs was greatly diminished He could turn in bed November 4th the patient was able to sit up in bed his grip improved there was not as much ataxia and he requested discharge from the hospital The treatment with liver extract and vegex was continued

On December 1st the patient appeared for examination, and stated that two and one half weeks after discharge he was able to walk On this date he was somewhat ataxic—both upper and lower extremities Astereognosis is less marked the station is improved his knee jerks are still absent grip is equal and good finger to nose test almost normal he is able to write his name Two weeks later he returned to work and drove his automobile

On repeated examinations steady improvement was noted April 15th he

walks perfectly, his grip is excellent, there is no ataxia of either extremity, there is no astereognosis, his strength has returned, the knee jerks are absent, the Babinski, which was present at one time during his stay in the hospital, has disappeared, his station is normal. He states that there is still slight numbness in the left hand.

His blood count while in the hospital showed steady improvement, so that on discharge November 2d it was 100 per cent hemoglobin, 5,410,000 red blood cells, 9500 white blood cells, differential within normal limits. The reticulocytes increased on October 16th to 5 per cent. April 25th his hemoglobin was 107.4 per cent (H H), red blood cells 6,100,000, white blood cells 7500, differential normal. No evidence of macrocytosis was present.

Discussion—In an authoritative article Strauss *et al*¹⁰ have presented the results of treatment in a large series of cases. Not one of the patients in whom there were no signs or symptoms of nervous system involvement developed them. Every patient with signs and symptoms of nervous system involvement was improved and has remained improved under their treatment. They conclude that the administration by intramuscular injection of solution liver extract—Lilly—in amounts of 10 cc twice a week as the maximum, 10 cc once a week as the average, and 10 cc once in three weeks as the minimum is most efficacious. They state that a dose of 10 cc per week is the equivalent of 5000 Gm of liver per week or 714 Gm per day. This emphasizes the importance of large doses in the treatment of these complications. In our clinic since liver extract for parenteral use was developed we have not used any other form of treatment for pernicious anemia. None of our patients have developed evidences of nervous system involvement as long as they have received adequate treatment.

The patient (A E) mentioned in this report received 3 cc of Lederle's liver extract intramuscularly daily, as well as the other materials mentioned in the report. As his symptoms and signs progressed, even under what seemed to be adequate treatment, it was imperative that something more be done, and accordingly fever therapy was used. The improvement was dramatic. To ascribe this entirely to the fever therapy is an exaggeration. It may be that the improvement from the use of liver extract and liver by mouth had been delayed for some

reason and that the good results obtained were due not so much to the fever therapy as to the liver therapy. The suggestion made by Drs. Castle and Strauss that this patient may have had multiple sclerosis we feel is untenable. The patient has pernicious anemia. We failed to estimate the colloidal gold curve in the spinal fluid because we had no thought of the presence of multiple sclerosis. However, it seems to us that other signs and symptoms of that disease are lacking in this patient. At present he is eating small amounts of liver daily and receiving an injection of liver extract once in three weeks.

In patient K. M., who did not receive adequate liver extract therapy because it was not available, we feel certain that the fever therapy given her resulted in definite improvement in the signs and symptoms of nervous system disease.

Our conclusion, therefore, is that the preferable form of treatment is that set forth by Strauss. There seem to be, however, a few patients in whom some of these other methods of treatment will prove beneficial.

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THE TREATMENT OF THE SO-CALLED "SECONDARY ANEMIAS"

THE term "secondary anemia" has been applied with such variable meaning to so many different types of anemia, that it has ceased to have much scientific significance. The usual connotation of "secondary" implies an anemia of low color index or microcytic type secondary to some obvious "cause." It is sometimes applied to any nonaddisonian anemia even though many nonaddisonian anemias are just as truly "primary" as pernicious anemia itself (*e g*, chlorosis).

Furthermore, the fundamental basis of separation between "primary" and "secondary" is no longer valid. Pernicious anemia may be "secondary" to some "liberating" cause such as gastric polyposis, gastric carcinoma or surgical gastrectomy.¹ The majority of cases of pernicious anemia are "primary" only in the fact that the cause of the intrinsic deficiency is unknown. Finally, there is the added confusion of designating many anemias due to certain primary blood system disorders (*e g*, leucoses) as "secondary" in type.

Our classification of the anemias from the standpoint of mechanism of causation is as follows: (1) Posthemorrhagic (blood loss), (2) hemolytic (destruction of blood), (3) aplastic or dysplastic (disturbed formation of blood).

The posthemorrhagic anemias include those due to acute or chronic blood loss, the causes of which may be legion.

The hemolytic anemias include hemolytic ictero-anemia, sickle cell anemia, some of the anemias of infections and in

festations, of various chemical intoxications, of serum hemolysins and malignancy

The aplastic and dysplastic anemias include the various "deficiency" anemias (pernicious anemia, sprue, anemia of pregnancy, "chlorosis," "hypochromic anemia," "nutritional anemia," avitaminoses, celiac disease, gastro-intestinal polyposis, etc.), certain anemias of infancy (premature infants, Cooley's anemia, von Jaksch's anemia), the anemias of bone marrow malignancy (metastasis, leucoses), the so-called "aplastic" anemias (both primary and secondary), Banti's disease, Gaucher's disease, osteosclerotic anemia, etc

In any given case of anemia, the mechanism may overlap (*e g*, pernicious anemia is not only a dysplastic anemia, but is also a hemolytic anemia, and may at times be partly posthemorrhagic)

The first and most important step in the successful treatment of anemia is to determine its cause or causes and its mechanism as accurately as possible. In most chronic anemias there are multiple etiological factors

The great advances of recent years do not justify the easy "shotgun" therapeutic methods that are now too much in vogue. The type of deficiency (iron, antianemic liver principle, vitamin) should be determined. Present-day methods include and demand a "specific therapeutic test" of the provisional diagnosis. "The failure to obtain a satisfactory blood response from adequate pernicious anemia therapy in any patient with a well-marked anemia is now generally accepted as good evidence against the diagnosis of pernicious anemia in such a patient"¹ Exceptions to this generalization include complicating infection, arteriosclerosis, insufficient dosage, material lacking in potency, or failure to use parenteral route in certain cases. The same rule with exceptions holds true for adequate iron therapy in iron-deficiency anemias

Double-barreled therapy (*e g*, vitamin, iron, liver, copper combinations) has a place, but only in the face of demonstrated multiple deficiency, or of absolute failure to work out the actual state of affairs

Iron Therapy—The indications for iron administration include posthemorrhagic anemias, idiopathic hypochromic anemia, chlorosis, nutritional anemias, hypochromic anemias of pregnancy, anemia secondary to infection, infestation and intoxications, and hypochromic anemias in general

The term "chlorosis" is confusing because it is applied to a variety of low color index anemias (with or without achlorhydria) The reader is referred to Stengel's Edition of *Nothnagel's Encyclopedia of Medicine* (Saunders) 1905, for a description of classical chlorosis, and to Fitz Hugh's chapter on "Chlorosis" in the *Cyclopedia of Medicine* (Davis Co) 1933, for detailed description and comparison of the modern concept of chlorosis The treatment of chlorosis may serve as a text for iron therapy of anemia in general

Unlike liver therapy, iron is of little or no value when given hypodermically It is impossible to give sufficient amounts of any present-day preparations of iron, parenterally, without producing pain or other untoward reactions² The normal human body contains about 3.5 Gm of iron,³ most of which is combined with hemoglobin The average iron content of the blood ranges from 44.84 mg per 100 cc. in normal young men to 42.48 mg per 100 cc. in normal young women.⁴ The body requires normally from 6 to 12 mg of iron daily to replace the iron which is lost through daily hemoglobin destruction (bile pigment syntheses) for new hemoglobin formation In hypochromic anemia, the body needs 32 mg of *metallic* iron *daily* to produce maximum amounts of hemoglobin² More iron is necessary in many cases Approximately all iron administered parenterally is absorbed Only a small portion of iron taken by mouth is utilized Excessive doses orally are necessary to produce a successful therapeutic response Approximately 1000 mg of metallic iron (in the form of iron and ammonium citrate—6 Gm) is considered adequate when administered orally daily It is equivalent in blood building power to 32 mg of *metallic* iron when administered hypodermically *daily*² (0.2 Gm or 3 grains of iron and ammonium citrate yield 32 mg of *metallic* iron) A survey of popular present-day

parenteral iron preparations shows, on this basis, that none contain adequate dosage. Parke, Davis & Co make ampules each containing from 0.015 Gm ($\frac{1}{4}$ grain) to 0.097 Gm ($1\frac{1}{2}$ grains) iron citrate in solution, yielding from 2 to 16 mg of *metallic* iron respectively. Fraisse's ferruginous ampules contain iron cacodylate 0.01 Gm ($\frac{1}{6}$ grain) yielding 0.0015 mg or $\frac{1}{48}$ grain of *metallic* iron. Zambelletti's ampules vary in strength from 0.0245 to 0.07 Gm of iron citrate in 1 cc of solution, yielding from 2 to 12 mg of *metallic* iron respectively. Even if 2 ampules of the above preparation of iron citrate, 0.097 Gm or $1\frac{1}{2}$ grains, were given *daily* it would not only be insufficient for many cases, but it would also be economically impossible for most patients in addition to the toxicity previously mentioned.

An average increase of 1 per cent hemoglobin per day is considered the index of successful treatment.⁵ The percentage increase is inversely proportional to the hemoglobin level at the time of treatment. The lower the hemoglobin (below 50 per cent) the more rapid the regeneration. A successful end-result of iron therapy, however, is sometimes compatible with less than 1 per cent average increase hemoglobin per day. During the first seven to fourteen days, the earliest response to iron may be seen in the reticulocyte rise, which is similar to, though not as predictable as the "reticulocyte crisis" in liver therapy of pernicious anemia.

The ideal of iron therapy is to obtain maximum absorption of iron in such form as to be most easily utilized in hemoglobin production. It has been recently shown that absorption depends in part at least on the liberation of ferrous ions within the gastro-intestinal tract.⁶ Indeed the present trend of evidence suggests that only that part of the iron which is reduced to an ionizable ferrous salt is useful in hemoglobin production. The rest is apparently inert or unabsorbed. The result of these studies has been to direct clinicians more toward the use of ferrous salts (ferrous sulphate, ferrous chloride, ferrous carbonate) in the treatment of iron deficiency. Apparently one may obtain a maximum effect from much smaller doses than

The effective adult dose of ferric salts in the form of iron and ammonium citrate ranges from 4 to 8 Gm. in divided doses, per day. The chief disadvantage in this and other large dose preparations of iron is their tendency in some patients to produce dyspepsia, colicky diarrhea or constipation. Ferric ammonium citrate is usually well tolerated by infants. Joseph¹⁰ uses a 10 per cent solution of ferric ammonium citrate—2 cc per kilo body weight, either alone or in milk.

Ferrous salts in the form of ferrous carbonate saccharated capsules, or Bland's pills in doses of 3 to 4 Gm. (45 to 60 grains) per day are efficacious and well borne. There is no disadvantage in Bland's preparation except that stale pills pass unchanged through the gastro-intestinal tract. Parsons¹¹ has suggested a solution of ferrous sulphate in glucose syrup as a palatable, easily preserved preparation for infants. The following prescription might be useful:

℞ Ferri sulphas (precipitated)	12.8 Gm.
Solution glucose—75 per cent	160 cc
Sig.—One teaspoonful in milk or water t. i. d.	

Fullerton¹² recently reported his results of successful ferrous sulphate therapy in doses of 9 grains per day. From this he obtained the standard 1 per cent hemoglobin increase per day in most of his cases.

Ferrum reduction (metallic) is often well tolerated by both adults and children. Efficient adult dosage ranges from 1.5 to 3 Gm per day. It is best given in large capsules. For infants Merritt and Davidson advocate 0.05 Gm per kilo body weight.

In the minimum recommended daily doses, the minimum retail cost of the several iron preparations is approximately as follows: Iron and ammonium citrate capsules each 0.5 Gm ($7\frac{1}{2}$ grains) No. VI—9 cents per day, iron and ammonium citrate 25 per cent aqueous solution 180 cc (6 ounces) 24 cc— $12\frac{1}{2}$ cents per day, capsules ferrous carbonate saccharated each 0.65 Gm (10 grains) No. V—5 cents per day, Pil Bland's No. 12—3 Gm (5 grains)—10 cents per day, Feosol S. K. F. preparation of ferrous sulphate tablets No. IV each 0.2 Gm (3 grains)— $3\frac{1}{4}$ cents per day, ferrum reduction capsules each 0.65 Gm (10 grains) No. III— $4\frac{1}{2}$ cents per day.

Liver and Liver Extract—Except in rare cases, liver extract has no great hematopoietic value in the treatment of hypochromic or low color index anemias. In other words, put to the "specific therapeutic test" liver will not prompt a reticulocyte rise comparable to iron therapy in these cases. Bethel *et al*¹⁴ have conclusively shown equally good results with adequate iron therapy as compared with reports from the use of combined iron and liver or ventricle extracts. What little value there may be from liver therapy supplementing iron in the treatment of these anemias can probably be attributed to the high protein and high vitamin content. In occasional cases of achlorhydric hypochromic anemia there is a definite double deficiency, which is most effectively and economically controlled by continuous iron therapy supplemented by a weekly to monthly hypodermic injection of liver extract.

The "secondary anemia" fraction of liver (Whipple) is entirely different from Minot or Cohen's pernicious anemia fraction. It has not proved to be of any real value in the treatment of human anemias.

One occasionally sees pernicious-like anemias associated with cirrhosis of the liver,¹⁵ gallbladder infection,¹⁶ celiac disease (Gee's disease¹⁷), chronic colitis,¹ certain anemias of preg-

nancy,¹⁸ sprue¹⁹ and *Bothriocephalus* infestations, in which there is, along with other factors, a deficiency of antianemic principle. These patients respond to liver extract (fraction G of Cohen) therapy either alone or in addition to iron, hydrochloric acid, or vitamins. A recent report²⁰ of the use of large doses of liver extract (fraction G) in anemia suggests that it is worthy of trial in the prevention of the hemolytic crises, and in the management of individuals who refuse splenectomy. Also during a short period of observation in a case of Gaucher's disease with macrocytosis, liver proved useful. We have never been convinced that liver therapy was of any value in these conditions.

Vitamin Therapy—Deficiency of vitamin A and D leads to the development of rickets and its anemia. The response to cod liver oil, proper diet and iron is sometimes dramatic. Scurvy, with its hemorrhagic manifestations and anemia responds satisfactorily to orange juice, tomato juice or ascorbic acid. In the treatment of idiopathic thrombocytopenic purpura, therapy with vitamin A, D and particularly C is worthy of trial. The value of vitamin B₂ (present in liver, yeast and germinating cereals) is well recognized in the treatment of pellagra, sprue and other deficiency states. Certain cases of von Jaksch's and Cooley's anemia, and also Gee's disease classified in the nutritional deficiency group, improve on high vitamin therapy. Lucy Wills,²¹ working with pregnancy anemia in India, noted the curative effect of vitamin B₂ therapy (yeast or liver) in these cases. It was once thought that B₂ was the "extrinsic factor" of Castle, but more recent studies have proved this assumption to be incorrect.

Antianemic Dietary—Most authorities emphasize the importance of diet regulation in the treatment of idiopathic hypochromic anemia. Our experience is like that of Bethel who says "most of our patients, before coming under observation have had a reasonably adequate and well balanced diet, however, an occasional individual has been seen with achlorhydria and without a history of blood loss who has presented an anemia of secondary type. Such patients are usually elderly

and the diet may have been inadequate over a period of many years. It is in this group that we feel dietary corrections to be of particular importance. In the treatment of iron deficiency anemias we do not believe that any diet is of specific benefit."

The "nutritional anemias," those occurring in infants and children maintained on a strictly milk diet, and in adults on prolonged ill-balance dietary, whether medically prescribed or fad dictated are largely iron-deficiency anemias which respond to iron medication. Josephs¹⁰ treated a number of nutritional anemias in infancy with iron plus a milk diet and found that the speed of recovery was fully as good as a second group he treated with iron plus an antianemic diet consisting of fruit, vegetables and eggs. However, in cases where diet needs emphasis, the daily menu should include a variety chosen from the following articles of food. From 200 to 500 Gm daily of calves' or beef liver, or kidney (300 Gm of fresh liver contains approximately 21 mg of iron), plenty of apricots, peaches, prunes, apples, orange and tomato juice, leafy greens and salads, also high vitamin foods. Wheat germ and cod liver oil. The diet should be high in meat protein, the carbohydrate and fat content of the diet should be relatively low.

Ultraviolet Ray—The effect of sunlight or ultraviolet lamp on blood regeneration is obscure. It is perhaps, if judiciously employed, of some general tonic value, but it is by no means specific and is rarely of great importance.

α -Ray and radium therapy are used to stimulate erythropoiesis in some of the aplastic and dysplastic anemias. α -Ray and radium therapy are of most benefit in the so-called "secondary anemias" associated with the leucoses and bone marrow malignancies.

Surgical Treatment—(a) *Focal infection* must sometimes be eliminated before complete success can be achieved in the treatment of anemia. Infection inhibits the utilization of iron and of the antipernicious anemia liver factor. The presence of infection not only may cause blood destruction, but may also inhibit and depress blood formation. The more

common anemia producing infections of silent type are pelvic inflammatory disease, cholecystitis, dental and tonsillar sepsis and *Streptococcus viridans* endocarditis

(b) *Treatment of the Cause*—The cooperation of the surgeon is obviously of prime importance in the final cure of most cases of posthemorrhagic anemia of chronic or recurrent type, hemorrhoids, fibromyomata uteri, peptic ulcer, epistaxis, hematuria, internal hemorrhage, etc

(c) *Splenectomy* is a brilliantly successful measure in selected cases of hemolytic ictero-anemia and severe fulminating or chronic thrombocytopenic purpura.

Transfusion of blood is often an emergency measure of supreme importance in anemia of various types. It is also of great value in preparing an anemic patient for some necessary operative procedure. In acute febrile hemolytic anemia, transfusions seem to be specifically curative.

Copper—Certain authorities²³ consider copper to be an important hematopoietic catalyst. The human body apparently needs minute traces to carry on its activities. However, almost any diet contains sufficient amounts to meet these mineral needs. A deficiency of copper (along with iron) possibly may exist in the anemia of infants caused by unsupplemented milk diet, but proof is lacking of the importance of copper in all other human anemias. Josephs²⁴ reported a series of nutritional anemia cases in which iron with copper supplemented gave results which he considered superior to those obtained from iron alone. In a larger series of anemias of all types Sachs *et al*²⁵ have found high copper values. When blood iron values return to normal, copper values decrease and *vice versa*. The experience of our clinic leads to the conclusion that copper medication has no value in the treatment of anemic adults. The work of Drabkin, Fitz Hugh and Robson² indicates that even in the milk anemia of rats, copper plus iron is no better than glutamic acid plus iron.

Arsenic.—"In anemia arsenic has long had an excellent reputation as a hematinic, but the evidence is far from clear."

The anemia of myeloid leukemia may undergo remission under arsenic (Fowler's solution) therapy

Bile Pigment—Minot and Patek²⁷ recently suggested that both bile pigments and purified chlorophyll will enhance the potency of suboptimal doses of iron in idiopathic hypochromic anemia. They used a dose of 2 Gm daily of a specially prepared (E Lilly Co) capsule of bile pigments

Endocrine Therapy—Thyroid gland substance is of value in certain cases of hypothyroidism with anemia. The female sex hormone of the anterior lobe of the pituitary is useful in the control of functional uterine bleeding of young women—a condition which not infrequently causes severe "chlorotic" type of anemia. The experience of this clinic with the use of ovarian substance and other female sex hormone products in the treatment of hemophilia (which causes anemia only by hemorrhage) has not been favorable

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PERNICIOUS LEUKOPENIA (AGRANULOCYTIC ANGINA) CLINICAL AND EXPERIMENTAL BACKGROUND AND PRESENT STATUS

IN 1922, Werner Schultz¹ in Berlin described what he believed to be a new and fatal disease of elderly women characterized by necrotizing oropharyngeal infection, fever, prostration, slight jaundice and profound leukopenia, due to complete or nearly complete absence of granulocytes, without anemia or thrombocytopenia.

During the twelve years that have elapsed since this report a voluminous literature has accumulated so that there are now more than 600 cases on record from this continent alone, the majority of which have been reported during the past six years. During the years 1931, 1932 and 1933 over 1000 death certificates of this disease have been filed with the United States Bureau of Vital Statistics.²

Schultz's original characterizations were soon found to be too restricted, especially as to sex, age, and mortality, although the disorder is still recognized as most common in adult women and still carries a death rate of well over 50 per cent in the combined statistics.

Schultz proposed the designation agranulocytosis, later rechristened agranulocytic angina by Friedemann.³

Although profound leukopenia, from overwhelming sepsis, had been previously described by Türk in 1907, and aleukemic leukemia and aplastic anemia had long been recognized, the syndrome of Schultz represents a valid "discovery."

Several questions arose at once Was agranulocytic angina a disease entity? Had it actually been spawned *de novo* in the twentieth century? Or was it merely a newly discovered antique?

These questions have not yet received final answer Many observers (including the writer) believe the disorder to be a valid clinical entity or syndrome "in the same sense that pernicious anemia is recognized as such" ⁴ Others think it is "not an entity" but rather a "deficient response of the patient" to a variety of causal factors ⁵ This disagreement is more apparent than real and depends upon definitions Bronchial asthma and pernicious anemia are generally admitted to be nosologic entities yet each may represent a "deficient response of the patient" to a variety of factors A third group believes that so-called "agranulocytosis" is not a specific disease entity at all but merely "a nonspecific reaction to" various infections "of unusual absolute or relative virulence" ⁶

That the disease or syndrome is essentially a twentieth century phenomenon is held by most observers although the suggestion has been made⁸ that ancient texts, prior to the era of blood counts, described it under such designations as "putrid sore throat" and "gangrenous angina" Personal opinion is, with the majority, that the disease is for the most part a new one with a rapidly increasing incidence An isolated report by Brown⁹ in 1902 concerning a fatal case of acute "primary" pharyngitis with extreme leukopenia may possibly represent the pioneer record of "Schultz's syndrome" in this country Brown believed, however, that his case was identical with those of "phlegmon of the pharynx" reported by Senator in 1888 In the 1901 edition of his "Clinical Hematology" Da Costa¹⁰ refers to "the most extreme instance of leukopenia on record" reported by Koblanck¹¹ in 1889 Koblanck "found but a single leukocyte in a careful search through 20 stained cover-glass preparations of blood from a man of twenty-five years suffering from epilepsy" This patient had a practically normal red cell count and necropsy yielded no satisfactory explanation of the cause of death—a most intriguing report for the present-

day student of "agranulocytosis" inasmuch as amidopyrine, now arch suspect, was not prepared until four years later *

NOSOLOGIC STATUS

The designations agranulocytosis (Schultz) and agranulocytic angina (Friedemann) have been generally adopted despite obvious objections. Agranulocytosis literally means either "increase of agranulocytes" or "absence of granulocytosis"—neither of which is descriptive of the essential hematologic feature. The adjective agranulocytic carries similar connotations and the designation angina (literally a strangling or choking) emphasizes an apparently secondary feature which is sometimes absent entirely. Other proposed names are primary granulocytopenia and idiopathic or primary or malignant neutropenia. These designations are etymologically unobjectionable and emphasize the most striking feature of the syndrome (paucity of granulocytes) but, according to the writer's view, they fail to suggest the fact that another characteristic feature is *paucity of all the leukocytes*, or leukopenia rather than merely neutropenia. For these reasons and because of the following clinicopathologic analogies to pernicious anemia the writer^{12 13} has suggested the designation *pernicious leukopenia*.

A COMPARISON OF PERNICIOUS ANEMIA AND PERNICIOUS LEUKOPENIA

1 Pernicious anemia is apparently a "conditioned deficiency" syndrome the intrinsic mechanism of which is lack, or destruction, or loss of a specific normal gastric function on which normal erythropoiesis and erythrocyte delivery are dependent (Castle).

Pernicious leukopenia is apparently a conditioned sensitivity syndrome the locus and modus operandi of the intrinsic

* Amidopyrine first prepared in 1893, was patented in Germany under the name "pyramidon" in 189. Although available in America as "pyramidon" since 1910 it was not until 1922 that American drug firms began to manufacture it under the pharmacopoeial name of amidopyrine.

mechanism of which is unknown This mechanism is probably concerned with normal leukopoiesis and leukocyte delivery

2 The pernicious anemia syndrome usually appears without obvious "cause" This primary type is probably due to a constitutional (hereditary?) defect of the intrinsic (gastric) mechanism which rarely becomes obvious before adult life is reached, which is subject to remission and relapse, and which may remain "latent" (*e g*, blood relatives of pernicious anemia sufferers) or only partially manifest ¹⁴

The pernicious leukopenia syndrome often appears without obviously sufficient cause This primary type is probably due to a constitutional¹⁵ (not obviously familial or hereditary) factor which rarely becomes manifest before adult life is reached, which is subject to remission and relapse, and which may remain latent or only partially manifest

3 The pernicious anemia syndrome is sometimes *apparently* produced by obvious "causes" (*a*) Destruction of the gastric factor (gastrectomy, polyposis, carcinoma, chronic gastritis), (*b*) loss of gastric factor and its interaction products (sprue, Gee's disease, intestinal parasitism, etc), (*c*) failure of storage of the gastric factor and its interaction product (liver disease), (*d*) absolute lack of the extrinsic factor (rare), and (*e*) various combinations of the above "conditioned deficiency" mechanisms It must be admitted, however, that a constitutional defect or predisposition to the disease may possibly be present even in those individuals whose apparent external causative factor seems quite adequate (*e g*, fish tapeworm anemia) It must also be emphasized that these cases of so-called "secondary pernicious anemia" ¹⁶ are prone to be atypical, or latent, or incompletely manifest

The pernicious leukopenia syndrome is sometimes *apparently* produced by obvious "causes" (*a*) Drugs (such as amidopyrine, dinitrophenol, arsenobenzol, etc), (*b*) vaccine injections (typhoid), (*c*) surgical trauma (especially dental extractions), (*d*) certain infections (kala-azar, miliary tuberculosis of the bone marrow), (*e*) Hodgkin's disease, aleukemic leukosis Some of these apparently secondary types of per-

nicious leukopenia are atypical. It must be admitted that an intrinsic or conditioning mechanism must be operative in all of these patients—whose disease is *apparently* "caused" by factors which generally do not produce this result.

4 Pernicious anemia in relapse phase exhibits megaloblastic hyperplasia of the bone marrow with peripheral anemia. It may terminate finally in "aplastic stage." A remission is signaled by the reticulocyte crisis. A patient with pernicious anemia may succumb during remission to a complication acquired during relapse.

Pernicious leukopenia in early relapse phase exhibits a relative myeloblastic hyperplasia (and probably an adequate supply of other leukocytic progenitors) with peripheral leukopenia.¹² It too, may terminate finally in aplastic stage ("necrosis" of bone marrow, etc.) A remission is signaled by the myelocyte crisis. The patient with pernicious leukopenia may succumb, even though hematologic remission is under way, to infection acquired during relapse phase.

5 The syndrome of pernicious anemia may not only be *apparently* "caused" by a number of diseases or factors but is simulated either clinically or hematologically by a still larger number of diseases. The final proof of the pernicious anemia syndrome depends upon the specific therapeutic test.¹⁰

The syndrome of pernicious leukopenia may not only be *apparently* "caused" by a number of factors but is simulated either clinically or hematologically by many other diseases. The approximate proof of the pernicious leukopenia syndrome rests (insecurely at best) upon clinical and hematologic grounds and upon the course of events. The nosologic status of pernicious leukopenia is today where that of pernicious anemia was before 1926.⁴

CONSIDERATION OF ETIOLOGY AND PATHOGENESIS

The original view that pernicious leukopenia is the result of specific bacterial destruction of granulocyte tissue in the bone marrow was soon found to be inadequate. In the first place the bacteria recovered from the local lesions, and from the

blood stream in certain cases, were obviously a heterogeneous and variable horde. Then it was found that many patients succumbed without blood stream invasion, and those with final septicemia frequently exhibited sterile blood cultures early in the course of the disease. Finally the demonstration of blood changes¹⁷ prior to actual clinical onset and prior to oropharyngeal ulceration completely revolutionized the prevailing point of view.

The next step came from study of the bone marrow. The earlier statements of the bone marrow pathology indicated a primary destruction or aplasia of the granulocytic cells and their progenitors. Observations in several fatal cases, however, led the writer, in collaboration with Krumbhaar, to express dissatisfaction with this primary aplasia hypothesis. We found in the bone marrow of patients who had just died of the disease, with antemortem leukocyte counts of from 200 to 500 white cells (all lymphocytes) a plentiful supply of myeloblasts and myelocytes. We were thus led to formulate an hypothesis of primary maturational arrest rather than primary aplasia to account for the facts of our cases. Our findings and tentative hypothesis have been extended and confirmed and generally adopted^{18, 19, 20}—although our proposed name “pernicious leukopenia” which immediately suggested itself has not found general favor.

The present day view of the pathogenesis of pernicious leukopenia is as follows. For some unknown reason, perhaps through a peculiar sensitivity reaction (O. H. P. Pepper) to certain drugs and other “toxins” with consequent suppression of chemotactic or maturational factors, there occurs first in the leukopoietic tissues of the bone marrow (and subsequently in the leukopoietic tissues of the lymph nodes, spleen, and other parts of the reticulo-endothelial system) a standstill or arrest of development of the parent white cells. Maturation and emigration slow down or cease entirely. Rapidly progressive leukopenia ensues with granulocytopenia predominating. The loss of this normal defense is quickly followed by tissue damage and bacterial invasion and widespread cellular necrosis. The

white cells of the bone marrow represented by nothing older than myeloblasts (and sometimes myelocytes) in normal or supernormal numbers (myeloid hyperplasia stage) may likewise finally suffer death and necrosis (so-called "aplastic marrow" stage). Death of the patient soon follows or a remission (partial or complete) ensues. The remission seems to be initiated by a "release of maturational arrest" or some other factor which allows normal leukopoiesis and emigration to occur. A flood of young granulocytes appears in the blood stream (Doan's myelocyte crisis) and, in a satisfactory remission, a relatively normal leukocyte picture is soon reestablished—with tissue recovery and convalescence following just a short step behind the hematologic process.

This sketch leaves many gaps in our knowledge and some of its outlines are suppositional rather than factual. Our contention that the bone marrow (and other leukopoietic tissues) in this disease may in certain cases at least be plentifully supplied with the progenitors of the white cells at the same time that the blood exhibits extreme leukopenia is now universally admitted. That the leukopenia may precede clinical symptoms in certain cases (Kracke *et al*) is also generally believed. It is not clear, however, that the primary disturbance is one of chemotaxis and leukocyte emigration or one of leukocyte maturation. Moreover, the excretion of leukocytes, via the saliva and gastro-intestinal tract, has not been sufficiently investigated in onset and recovery phases of the syndrome. Our studies⁴ were inconclusive as to this point. The actual destruction of circulating leukocytes as an important mechanism of the leukopenia has never been satisfactorily demonstrated.² The new observation of an immediate "granulocytoclastic crisis"²¹ which occurs within a few hours of the ingestion of a small dose of amidopyrine in certain individuals just recovered from an attack originally associated with apparent amidopyrine idiosyncrasy must, however, be taken into account in any generalization. This granulocytoclastic crisis may not be representative of the primary mechanism of a clinical attack, but if it is we shall have to assume it to be a transient episode hitherto

omitted from the three stages hypothesized by Kracke and appearing too promptly to be mediated by disturbed bone marrow delivery. From this standpoint the bone marrow mechanism might be assumed to exist in a damaged state (of "latent sensitivity"?) prior to the granulocytic crisis and be precipitated thereby into actual maturational arrest. Further study is urgently needed of this phenomenon.

Many "possible causes" of the syndrome have been set forth by various writers. The hypothesis of specific bacterial etiology has led nowhere. Bacterial allergy (*e g*, the Schwartzman phenomenon²²) remains, however, as a possibility. Several cases have apparently followed typhoid vaccine.²³ We have attempted to reproduce the disease in animals by various sensitization methods—employing various suspected bacterial strains and toxins—without success. We (Comroe and Fitz-Hugh—unpublished data) failed to confirm the experimental results of Dennis²⁴ who implanted intraperitoneally in rabbits sealed parchment capsules containing broth cultures of various pathogenic organisms. In acute anaphylactic shock in dogs, however, we have observed a marked leukopenia and granulocytopenia, which, while it lasts (to death or beginning recovery of the animal) simulates fairly closely the blood picture of Schultz's syndrome.

Other etiologic factors that have been suggested are: Congenital anomaly of hemopoietic tissue,¹⁵ fatigue,⁵ endocrine disturbance—especially cyclic variations in female sex hormone^{20, 27} and disturbance of the adrenal cortex hormone,²⁸ occasionally kala-azar,²⁰ therapeutic malaria,³⁰ miliary tuberculosis,³¹ acute leukosis, Hodgkin's disease and overwhelming sepsis, all of which may in rare instances either reproduce the syndrome or so closely simulate it as to be sometimes indistinguishable, and finally, a number of drugs, some of which deserve careful consideration.

DRUG ETIOLOGY

The writer has recently reviewed²¹ the evidence for and against the drug etiology hypothesis, with particular reference

forth really convincing evidence of the possibility of amidopyrine as a cause of the disease, the data tending to incriminate this drug have rapidly accumulated ^{7, 20, 21, 32-45}

All observers agree that amidopyrine, if it be of true causal significance, acts by way of a sensitization or idiosyncrasy mechanism, and that it is probably not the only cause. It is estimated* that 80,000,000 5-grain doses of amidopyrine are consumed yearly in this country on prescription alone (exclusive of hospital administration and over-the-counter dispensing). Obviously only one in many thousands is affected in the manner under consideration. That the noxious action is not an ordinary toxicologic²¹ one is proved by many other considerations. Normal leukocyte records of habitues, of lingering suicides, of many large-dose users, and the apparently overwhelming effect of relatively trifling doses in many cases of agranulocytic angina itself.

The same may be said of other drugs that have been recently incriminated as possible causes of the disease—including dinitrophenol,^{35, 46, 47} arsenobenzol,⁴⁸ "gold salts,"⁴⁹ quinine, orthoiodoxy benzoate,²¹ the so-called "benzamine group" of drugs discussed by Kracke,⁷ and neostibosan.²⁰

From a statistical standpoint the case against amidopyrine is the most impressive. The barbiturate group of drugs at first suspected along with amidopyrine has now been practically exonerated.^{30, 40}

Henry Jackson, Jr.,⁵⁰ who is, in my opinion, the most experienced and careful student of the problem of "agranulocytosis" has recently taken a somewhat uncertain stand against the current wave of evidence which would seem to incriminate amidopyrine. Although he admits that 26 per cent of his cases may possibly ("perhaps probably") have been actually caused by the amidopyrine known to have been administered, he feels that in another 30 per cent the associated amidopyrine medication could have had no causal relation to the disease and

* From the data of the Pharmaceutical Association published in 1933 and prepared by the National Formulary Revision Committee of the United States Pharmacopeia

that at best the diagnosis is sometimes uncertain and that some cases of aleukemic leukemia, panmyelophthisic and aplastic anemia, and overwhelming septicemia have been reported incorrectly under the designation of agranulocytosis. These strictures, however, have only slight bearing upon the problem of drug etiology. Jackson's most impressive evidence against the hypothesis of amidopyrine etiology is as follows. Five of his patients took amidopyrine during and/or after episodes of agranulocytosis without any depressing effect and with clinical and hematologic recovery, 12 patients, in his series of 27, received, he thinks, no drugs of the amidopyrine series whatsoever.*

This evidence of Jackson's, like that previously reported by the writer, proves that amidopyrine is not the sole cause of the syndrome. That it may well be a most important contributing cause, however, is suggested by the fact that more than 100 cases, thought by the reporting physicians to have been caused by amidopyrine medication, have been recorded in 1934†. In addition to such supporting facts as the twentieth century birth of the syndrome and its astonishing predilection for doctors, doctors' wives, nurses, technicians, dentists and other members of such drug-sample-saturated households,

* Since this was written Dr Jackson has made his views clearer in a personal communication (March 9, 1935) as follows: "My position therefore is not one of denial that amidopyrine is of great importance but rather one of conservatism as regards concluding that it is the sole cause."

† List of authors—with dates of publications—and number of cases reported of agranulocytic angina developing in connection with amidopyrine medication: Videbeck (May, 1933), 1, Costen (June, 1933), 2, Watkins (November, 1933), 13, de Vries (November, 1933), 1, Holten *et al* (February, 1934), 7, Jørgensen (February, 1934), 1, Zininger (February, 1934), 2, Seeman (March, 1934), 17, Andersen (March, 1934), 1, Madison and Squier (March, 1934), 14, Randall (April, 1934), 1, Hoffmann *et al* (April, 1934), 13, Larsen (April, 1934), 1, Sturgis and Isaacs (May, 1934), 7, Blumer (May, 1934), 1, Haden (May, 1934), 1, Kracke and Parker (May, 1934), 6, Rawls (June, 1934), 2, Zinberg *et al* (June, 1934), 1, Benjamin and Biederman (July, 1934), 1, Groen and Gelderman (July, 1934), 13, Fitz-Hugh (August, 1934), 17, Corelli (August, 1934), 2, Knudsen (August, 1934), 1, Jackson (October, 1934), 7, Moltke (October, 1934), 1, Johnson (October, 1934), 1, Spegler and Spigler (October, 1934), 1, Fisher (December, 1934), 1, Plum (January, 1935), 7. Total of 144 cases (90 + deaths) up to January, 1935.

there is the even more convincing observation of the phenomenon which I have called the granulocytoclastic crisis²¹ This was first observed by Madison and Squier and has since been recorded by others (Benjamin and Biederman, Sturgis, Plum, and Fitz Hugh) This phenomenon is typically as follows A patient recently recovered from an episode of agranulocytic angina presumably initiated by, or at least associated with, known amidopyrine medication is given a moderate dose of the drug (5 to 15 grains) The leukocyte count previously normal shows a precipitous drop to one half or lower within two to twelve hours—with loss of 30 to 90 per cent of the granulocytes Recovery is usually prompt (*i. e.*, within twenty-four hours) but may be delayed for seven days¹⁵ Following or paralleling the sharp neutropenia there may be, but not always, pyrexia, malaise, chill and sore throat This granulocytoclastic crisis comes too soon to be mediated by cessation of bone marrow activity and must be due to rapid excretion of neutrophils (via saliva and gastro-intestinal tract as suggested by Isaacs), rapid destruction, visceral and splanchnic retention, or by "sticking" of the leukocytes along the capillary walls (Clark) It would seem probable, moreover, that the sensitized bone marrow is sooner or later "shocked" into a state of maturational arrest by repetitions of this process Recovered patients have been similarly tested by administration of other suspected drugs such as acetylsalicylic acid, barbiturate compounds (alurate, amyral, etc.) and codeine sulphate without any untoward clinical or hematologic result I am not aware that any of the several cases of agranulocytic angina apparently due to dinitrophenol, arsenobenzol, quinine, oxoate, 'gold salts' or neostibosan have been similarly tested for sensitivity Theoretically one would expect a similar granulocytoclastic response A correlated observation, however, has been made in several cases of recurrent agranulocytosis The report of Wingate Johnson¹² is especially interesting His patient (again a doctor's wife) had several attacks of agranulocytic angina associated with the menses This might have been considered evidence of the alleged menstrual factor²⁷

but it was found that an amidopyrine preparation (cibalgine) was being taken for the first few days of each menstrual epoch and when this medication was stopped the succeeding menses were unassociated with leukopenia and the patient has since remained well

I am convinced that since wide lay and professional publicity has been given to amidopyrine as a probable cause of agranulocytic angina there has been a definitely decreased incidence of the disease. During the past ten months, from June 1, 1934, to the present time, April 1, 1935, I have seen only 3 cases—in 2 of whom amidopyrine medication had been given for several weeks immediately prior to discovery of agranulocytosis and in 1 prior amidopyrine medication was highly probable but could not be proved. During the preceding ten months (August, 1933, to June, 1934) I saw 6 cases

Skin sensitization tests ("patch" and "scratch") using amidopyrine and other drugs, foods, etc., have failed in our hands to show any significant reactions in a number of cases of agranulocytic angina (including negative amidopyrine skin tests in recovered individuals showing a positive granulocytoclastic crisis from amidopyrine). Others have reported similar failures to obtain positive skin reactions in a variety of known drug idiosyncrasies (dinitrophenol,⁵¹ arsenobenzol,⁵² amidopyrine,^{42, 45} etc.) More recently, however, Madison and Squier⁵³ have reported positive patch tests to amidopyrine in 2 of their patients

The nature of this supposed drug idiosyncrasy mechanism in pernicious leukopenia remains to be clarified. Kracke believes that incomplete oxidation products (hydroquinone, catechol, etc.) of the "benzamine group" of drugs are responsible for the noxious action on the bone marrow. He, however, postulates an idiosyncrasy mechanism in addition. The thought of possible "impurities" in the manufacture of amidopyrine products naturally suggests itself although nothing of this nature has been demonstrated

Attempts to reproduce the disease in animals have been almost as inconclusive with drugs (amidopyrine, etc.) as with

bacteria Comroe and Fitz Hugh fed amidopyrine to rabbits in doses of 10 to 20 grains daily per rabbit for many weeks without producing any *significant* effect on the leukocyte picture. Thinking that some sort of sensitization might thereby be induced we carried out the following experiment. Amidopyrine was mixed with horse serum and incubated for a week. The mixture was then repeatedly injected into the ear vein of rabbits (1 to 2 cc. doses of the serum containing 5 to 10 grains of amidopyrine). No important change in the blood picture occurred. Two months later the same rabbits were injected intravenously with an aqueous solution of amidopyrine but no anaphylactic phenomenon ensued and no significant variation of leukocyte content could be demonstrated. At present Comroe, working in my laboratory, is investigating the blood and bone marrow of rabbits treated with amidopyrine according to the technic of Miller⁶¹. The latter has recently reported from the Rockefeller Institute, that the bone marrow of 16 dogs fed amidopyrine (0.3 Gm per kilo daily) for four weeks or more showed uniformly striking changes. Suppression of myeloid cell maturation, marked decrease of granulo-

tinued until further evidence is at hand, and (6) its inclusion in proprietary mixtures should be either prohibited by law or prominently indicated on the label of every package

TREATMENT

If the trend of evidence continues in the same direction as at present it would seem that we doctors, with all good intentions, have practically created a new disease, a Frankenstein monster in miniature, which has with perverse "justice" turned to attack our own medical households above all others. If this be true the first principle of treatment is "primum non nocere" Avoid amidopyrine and be watchful of possible harm from other drugs (*e g*, arsenobenzol and dinitrophenol) This is a disease in which "symptomatic relief therapy" may prove to be worse than no therapy at all Local oropharyngeal care should be mild and conservative Transfusions of carefully typed blood, carefully administered, from fasting donors, are of real value The intramuscular injection of leukocytic cream (Strumia) is harmless and in some instances seems to be helpful The same may be said of pentose nucleotide (Jackson) and liver extract (pernicious anemia fraction) although personal experience with all of these methods of treatment leaves little or no basis for belief in their specificity α -Ray "stimulation" of the long bones is worthy of trial in hospitalized cases Calcium gluconate, orange juice, brewer's yeast tablets, bone marrow extract and cod liver oil are recommended If one takes the view that the disease is a drug sensitivity reaction a "logical" therapeutic approach is suggested along such line as follows Calcium, cod liver oil, adrenalin and ephedrine to combat the supposed allergic state Intravenous decholin-sodium, mild saline laxatives, adrenalin and high carbohydrate diet (with intravenous glucose if necessary) to stimulate choleresis and to promote "detoxification," "desensitization" and "elimination" with regard to the liver as a possible seat of allergic disturbance These suggestions are admittedly not "strictly scientific" I have not yet had an opportunity to apply them energetically without the admixture of one or more

of the other alleged specifics. In a disease as serious as this (23 of my 29 cases are dead) one hesitates to withhold any item of treatment which others have found to be helpful. The most hopeful treatment in the amidopyrine series is to stop amidopyrine. There have been no relapses during the past twelve months in 5 of my 6 surviving patients, each of whom ingested amidopyrine for variable periods of time immediately preceding the establishment of the diagnosis of "agranulocytosis." The other surviving patient has had several relapses. He took no amidopyrine either before or since the onset of his disease. He represents that "primary" form of agranulocytic angina which may have existed, unrecognized as a clinical entity, long before amidopyrine was ever heard of. His is the exceptional type, however, and represents, I believe, the very rare instance that we may expect to see in the not far distant amidopyrine-free future. He had recovered *spontaneously* from two typical bouts of agranulocytic angina before I started him on pentnucleotide. Since then two telegraphic appeals have been met with air mail shipments of pentnucleotide, the administration of which was also followed by recovery.

SUMMARY

Pernicious leukopenia (agranulocytic angina) is largely a twentieth century disease entity, based on a hitherto unobserved and still little understood idiosyncrasy or sensitivity mechanism, with a primary effect of maturational arrest of the bone marrow granulocytes and other leukopoietic tissues, with consequent profound leukopenia (which may also at times be initiated by a granulocytoclastic crisis) and secondary sepsis from invasion of "opportunistic bacteria." While the disorder may be precipitated by other "causes" than drugs, just as bronchial asthma has other "causes" than animal dander, the present-day evidence points to amidopyrine as the most important single external factor in the etiology. A reasonable suspicion of certain other drugs, for the most part structurally related to amidopyrine, is also entertained. And finally it is

believed that in a much smaller group of cases the syndrome is initiated by some perhaps similar "shock" mechanism of sensitivity reaction in leukopoietic tissues damaged in other ways

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CLINICS OF DRS MARY H LASBY, GEORGE C GRIF
FITH AND JAMES E TALLEY

CARDIAC CLINIC, PRESBYTERIAN HOSPITAL

HEART BLOCK, ITS FREQUENCY AND TREATMENT

We are aware that heart block as found electrocardiographically does not always manifest itself clinically, but the cases used in this study in frequency were culled from the Electrocardiographic Departments of the Pennsylvania, Presbyterian, Graduate and Woman's Hospitals of Philadelphia, and from our private patients. From a survey of 22,200 electrocardiograms we have gathered 500 cases diagnosed as heart block for study and analysis. The occurrence of 500 cases diagnosed as heart block among 22,200 electrocardiograms does not mean that there were only 500 electrocardiograms out of that number which showed heart block. There were many patients who had repeated electrocardiographic tracings, so that the total number of electrocardiograms showing blocks, regardless of the number of cases, was considerably larger than 500. One of the above hospitals started to make electrocardiographic studies as early as 1914, so that our survey covers a period of approximately twenty years. Our cases, therefore, go back to a period antedating by several years the advent of the American Heart Association research charts. Hence the clinical data of some of the earlier cases are incomplete, especially in regard to past infection.

We have, therefore, a rather large group, slightly more than 10 per cent of the cases, in whom the occurrence of any associated disease condition was undetermined. The study includes all grades of disturbances of both the auriculoventricular and intraventricular conduction systems. The distribution is as follows:

Disturbance in auriculoventricular conduction, 293

Disturbances in intraventricular conduction, 180

Disturbances in both auriculoventricular and intraventricular conduction, 27

Of the 293 auriculoventricular blocks, 140, or nearly 50 per cent, were or had been receiving digitalis at the time the electrocardiograms were taken

One hundred and thirty-two of the 180 intraventricular blocks were receiving digitalis

The grades of block among the auriculoventricular conduction disturbances occurred as follows

Simple prolongation of the P-R interval (more than two-tenths of a second), 222 cases

Sino-auricular block, 7 cases

Occasional dropped beat, or 2 1, or 3 1 block, 32 cases

Complete auriculoventricular dissociation, 32 cases

Among the 64 cases included in the last groups, *i. e.*, the 2 1, 3 1 and complete blocks, the Adams-Stokes syndrome occurred in 21 cases

Of the intraventricular conduction disturbances, 44 are cases of simple intraventricular delay, or, expressed electrocardiographically, show widening of the QRS complexes to more than one-tenth of a second. The remaining 136 are cases of complete branch-bundle block. The branch-bundle blocks of left axis deviation type number 120, as compared to 16 of the right axis deviation type. In other words, 88.3 per cent are left branch-bundle blocks according to the new nomenclature. White¹ found 176 of his 212 branch-bundle blocks to be of the left axis deviation type.

Our youngest case of heart block was sixteen months of age, the oldest ninety years. The age distribution of the group as a whole is best shown in Fig. 12.

The figures of the abscissa show the ages of the patients in decades (Fig. 12). Those of the ordinates show the incidence of cases. The shaded line gives the total number of blocks regardless of the type. The auriculoventricular blocks

¹ White, Paul D. Heart Disease, The Macmillan Co., Publishers

are represented by the broken line, the intraventricular blocks by the unbroken line, those which show both kinds of block by the dotted line

It is apparent that up to the fourth decade the auriculo-ventricular type of block occurs almost exclusively. This is, of course, accounted for by the fact that this lesion is the fre-

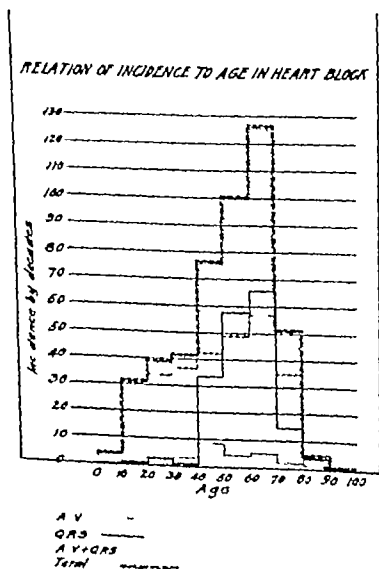


Fig. 17

quent concomitant of rheumatic infection. After forty there is a sharp rise in the incidence of the intraventricular type of conduction disturbances, as is to be expected on approaching the arteriosclerotic decades.

In discussing the classification of cases according to the associated disease present we have excluded all cases of auriculoventricular block which were receiving digitalis at the

time that their tracings were made, since the abnormality may have been due to the effect of the drug in such cases. We did not exclude those cases of intraventricular block which were receiving digitalis, since we believed from the clinical consideration of the cases that the blocks were not caused by the drug. It would be a matter of common procedure to speak of heart block as being due to associated infections known to cause heart disease such as lues or rheumatism, or to chronic diseased states such as arteriosclerosis, but as we have no proof that the associated conditions are the origin of the blocks themselves, we do not list them as etiological factors.

In addition to the cases receiving digitalis we have also excluded from this analysis those who had combined auriculo-ventricular and intraventricular blocks and a large group of cases which were not known to be associated with any of the conditions which are generally accepted as causes of heart disease. There remain 276 cases for consideration. Their distribution according to age groups is best seen in the following table.

Age	Cases of heart block occurring with congenital heart disease.		Cases of heart block occurring with rheumatic heart disease.		Cases of heart block occurring with luetic heart disease.		Cases of heart block occurring with hypertensive heart disease.		Cases of heart block occurring with arteriosclerotic heart disease.	
	A V	QRS	A V	QRS	A V	QRS	A V	QRS	A V	QRS
Up to 10 yrs	1		2							
10-20 yrs.			19	1						
20-30 yrs.	1		14	2	3					
30-40 yrs.	1		8	1	4					1
40-50 yrs.			9	10	2	3	2	5	2	8
50-60 yrs.			6	7	3	11	7	8	7	19
60-70 yrs			1	9	1	5	4	13	6	34
70-80 yrs					1		5	3	11	13
80+ yrs									1	2

It is apparent that up to the age of forty, practically all and were preponderantly of the auriculoventricular type

The blocks associated with luetic infection have their highest incidence in the fifth, sixth, and seventh decades and were almost equally divided between the auriculoventricular and intraventricular type. The blocks occurring with hypertensive and arteriosclerotic heart disease practically all occurred after the age of forty, and there were twice as many intraventricular as auriculoventricular blocks in these groups.

There was a group of 38 cases not included in this analysis because they were not associated with conditions commonly considered the cause of heart disease, but which were known to have had some other infection or chronic disease at the time that their electrocardiograms showed chronic disturbances.

Two of these patients had pneumonia, eight had either acute or chronic nephritis, five had hyperthyroidism, fifteen were diabetics, one was recovering from a ruptured ectopic pregnancy, one had encephalitis, one influenza, one abscessed teeth, three had arthritis, and one pulmonary tuberculosis.

There are certain considerations of the group as a whole which are of some interest. Ninety five, or 19 per cent, had family histories which were significant from a cardiovascular standpoint. Seventy four, or about 15 per cent, were definitely over weight. Three hundred and twenty-nine, or about 66 per cent, had had at some time definitely known foci of infection. These included abscessed teeth, diseased tonsils, prostates, and gallbladders. Twelve, or about 2.5 per cent, had hyperthyroidism. Three hundred and twenty-nine, or 66 per cent, showed definite cardiac enlargement. One hundred and eighty-one, or 36 per cent, had an established hypertension. Two hundred and twenty-three, or 45 per cent, showed some degree of congestive failure. One hundred and fifteen, or 23 per cent, had anginal pain. There were 14 cases of auricular flutter in the group. Thirty of the total 500 cases, or 6 per cent, were known to have diabetes mellitus. Seventeen of these showed auriculoventricular and intraventricular block.

An effort was made through the social service departments of the hospitals to follow up a certain number of the cases which had been lost sight of. Only a relatively small number of the earlier patients could be traced, and any discussion of the outcome of our cases is necessarily incomplete.

One hundred and thirty-two are known to have died. The causes of death are as follows:

Congestive heart failure, 70

Acute pulmonary edema (left-sided failure), 9

Pulmonary tuberculosis, 2

Subacute bacterial endocarditis, 1

Following operation, 3

Pulmonary embolism, and pulmonary thrombosis, 2

Embolism elsewhere than in the lungs, 1

Acute coronary thrombosis, 6

Carcinoma, 2

Acute nephritis, 4

Sudden death, probably from some cardiovascular accident, 7

Pneumonia, 4

Unknown, 21

Two of those included in the unknown group had Stokes-Adams attacks, but it could not be determined whether or not they died in such an attack.

Among the 132 known deaths were 54 cases of branch-bundle block. The average time of death after discovery of the block was eight and eight-tenths months, but we have no way of knowing how long the block had existed prior to the first electrocardiographic discovery of its presence, except in one case. This one case developed the block while under observation, and died exactly twelve months later.

Three hundred and sixty-eight cases are living, as far as is known. Eight cases were noted as leaving the hospital unimproved after long hospitalization. Two hundred and forty-four cases were improved when last seen, but have been lost sight of, *i. e.*, they have not been in clinic or elsewhere for a period of twelve months or longer. Of the 116 cases with

whom we are still in contact, 43 show no definite evidence of congestive heart failure, and are provisionally classified as Class I or IIa. The remaining 73 show moderate to marked congestive heart failure, being classified as Class IIb or III.

Summarizing our analysis of 500 cases diagnosed as heart block we find the following

Two hundred and seventy two of the patients were receiving digitalis at the time of the study. After excluding the digitalis cases showing auriculoventricular block and the group showing both auriculoventricular and intraventricular block, as well as those cases not associated with conditions known to give rise to heart disease, the remainder of the cases were analyzed from the standpoint of associated disease. The rheumatic group occurred largely in the early and middle decades, and included more auriculoventricular than intraventricular blocks. The luetic group occurred in the middle decades and contained a few more intraventricular than auriculoventricular blocks. The arteriosclerotic and hypertensive groups were found in the middle and advanced decades and contained many more intraventricular than auriculoventricular blocks.

There were 21 cases of Stokes Adams syndromes found in this study.

THE TREATMENT OF HEART BLOCK

Rarely does simple prolongation of the P R interval cause symptoms and, for the most part, it needs no treatment. If, however, two to one, three to one, or complete block occurs and is accompanied by Stokes-Adams symptoms the treatment is twofold. In the first place it must be determined by the etiological factor. Should it depend on digitalis effect, the dosage should be decreased or the use of the drug discontinued. If it is due to an active rheumatic process, to diphtheria or other acute infectious disease, or to cardiovascular lues, treatment must be directed toward the underlying infection. If the block is caused by arteriosclerosis, iodides and vasodilators are indicated. Secondly, treatment of the block itself can be attempted. This consists in an effort to remove

vagus effect by the use of atropine sulphate, in doses of from $\frac{1}{75}$ to $\frac{1}{25}$ grain. In the case of Stokes-Adams syndrome treatment is aimed at increasing the irritability of ventricular muscle. Several drugs have been employed for this purpose. The best drug to use in an attack is epinephrine hydrochloride (adrenalin) in doses of 4 to 8 minims in a 1:1000 solution intramuscularly, intravenously or even intracardially. When a heart has stopped, whether it be during anesthesia or a Stokes-Adams attack, intravenous or subcutaneous injections are useless. Five to 15 minims should be injected directly into the heart. Though this procedure is so rarely necessary, it is well to have a method in mind. Select the fourth intercostal space, at the upper border of the fifth rib, close to the sternum. Use iodine. Take a long, thin needle, 6 to 10 cm in length. Insert as far as the posterior sternal margin, incline slightly in a mesial direction, push in 4 to 5 cm. After some blood is aspirated, make slowly the injection of 1 cc adrenalin. Movements of needle due to cardiac contractions are favorable. One reaches the right ventricle by this method. By this site injury of internal mammary artery and pleura is avoided. The fine needles largely preclude injury of coronary vessels or conducting system.

After the successful administration of this drug to break up an attack, ephedrine sulphate or hydrochloride may be given as a preventive against further attacks. A common dose is $\frac{3}{8}$ grain by mouth every three to four hours. However, the well-known tendency of this drug to cause urinary suppression and retention in some individuals suggests the advisability of starting with a dose such as $\frac{1}{8}$ grain and carefully working up to the larger dose. Some caution should be exercised in the use of ephedrine in hypertensive cases except in those instances where there is not sufficient arteriosclerosis present for a moderate rise in blood pressure to cause difficulties. The use of thyroid extract as a ventricular irritant has given satisfactory results in a large number of cases. The dose varies from $\frac{1}{2}$ to 3 grains daily, according to the individual tolerance of the patient. Care must be exercised in dosage

if the patient at all suggests a myxedematous condition. In these patients too large doses may precipitate cardiac pain. Barium chloride in doses of $\frac{1}{2}$ to $\frac{5}{8}$ grain by mouth has been recommended but we have never found it of marked benefit in our own experience, however, it should be tried.

The occurrence of sino-auricular block rarely needs treatment beyond the correction of the toxic states which usually underlie its presence. If, however, sino-auricular standstill proves to be of sufficient severity as to distress the patient, ephedrine hydrochloride in the dosage described above will usually give prompt relief. Its action is, of course, to increase ventricular irritability. Atropine sulphate to relax vagal control may be useful.

The treatment of intraventricular block is similar to that of other types of heart block with emphasis on the use of iodides and coronary vasodilators, since this condition is most often of arteriosclerotic origin. The form of iodide therapy which we prefer is potassium iodide in doses of 5 grains, three times a day. This dose can be increased to the individual need of the patient. Nitroglycerin, sodium nitrite and other forms of nitrites may be substituted for this. Another group of vasodilators are the purine derivatives. Those most frequently employed are theobromine in doses of 5 to $7\frac{1}{2}$ grains, diuretin (theobromine sodium salicylate) in doses of 5 to 15 grains, and theophylline ethylenediamine (also known as metaphyllin, euphyllin, aminophyllin, thephyldine) in doses of $1\frac{1}{2}$ to 3 grains three times a day. Theocalcin, $7\frac{1}{2}$ to 10 grains, theominal (a combination of theobromine, 5 grains, and luminal, $\frac{1}{2}$ grain), and phyllicin (theophylline calcium salicylate) tablets of 4 grains each, one after meals, all have a similar action and are frequently used with good results. At least one is using remedies which experimentally have increased coronary flow. It is better to give them after food and where this is not possible, at least give them with a glass of water, because of their tendency to disarrange the stomach. In case of need these preparations may be given by suppository, by intramuscular injection or even intravenously with care.

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THE TREATMENT OF HYPERTENSION WITH SPECIAL
REFERENCE TO THE MANAGEMENT OF VASCULAR
CRISES

like pneumonia or typhoid fever should not be drawn from what I have said. It is a symptom or sign occurring in various conditions and induced by many factors. Controversy has raged concerning the etiology and classification of hypertension. From the standpoint of preventive medicine, the etiology is doubtless of considerable importance. When once established, however, the principles of management of high blood pressure are much the same whatever the cause may be, while the treatment of complications differs not at all. In recent years many writers have adopted the term hypertensive cardiovascular renal disease as a descriptive diagnosis. Others continue to call the syndromes in which it occurs by such names as essential, arteriosclerotic, benign, and malignant hypertension, since they present typical clinical features. I have selected cases which illustrate some of the common conditions met with.

The most serious of all types of high blood pressure is that which Volhard^t has called malignant hypertension. It occurs more often during the third or fourth decade, but may be found in children. In most cases it is due to or associated with glomerulonephritis, and in the later stages the blood vessels in the kidney like those in the retina and elsewhere are markedly diseased. The etiology is obscure. The nephritis is often caused by infections, such as scarlet fever, by lead, as was found in Queensland, Australia,¹ or by other toxic substances. How the hypertension and vascular changes are brought about is unknown. The course is influenced but little by treatment, the condition progressing till death from an intercurrent infection, from congestive heart failure, or from uremia supervenes. In some instances, no serious renal disease is demonstrable, although from the clinical picture a diagnosis of malignant hypertension may be made.

Such a case is that of Edward J., eleven years of age, whom I first saw in November, 1933. His complaints were headache, lassitude, and indigestion. He had suffered from hay fever and asthma since the age of three, had had mumps, chickenpox and whooping cough, and an operation for the relief of sinusitis two years previously. During the summer of 1933, he began to have headaches and his mother noticed a preference for lying about the house and reading.

rather than playing with his companions. In the next few months the headaches increased in frequency, he lost his appetite, complained of heartburn and nausea and developed obstinate constipation. He had never overcome the habit of bed wetting but the tendency to enuresis had recently increased. His sleep was often disturbed by nightmare. There was no family history of hypertension. His father was allergic to certain foods.

Physical examination showed him to be a pale, somewhat oversized boy weighing 88 pounds. The blood pressure was 144 systolic and 110 diastolic. The eyegrounds were negative. The heart was somewhat enlarged, the apex beat being felt a little outside the nipple. The aortic second sound was loud and ringing. The radial arteries were palpable but soft.

The blood count was normal, the blood urea nitrogen 9 mg per cent, the blood Wassermann negative. Repeated urinalyses showed a specific gravity of 1.016 to 1.023, no albumin in the morning specimens and a trace in those passed later in the day, very rarely a few hyaline casts, but no erythrocytes. The quantity of day urine during a modified Mosenthal test was twice that passed at night, and the concentration was normal. Phenolsulphonethylphthalein elimination was good. He was found to be sensitive to a number of pollens, to house dust and to various foods and animal emanations. \pm Ray and clinical examination revealed a chronic sinus infection which was later treated successfully by an otolaryngologist.

The treatment prescribed was an increased amount of rest, small doses of the elixir of phenobarbital for his nervousness, and a diet which eliminated condiments and the foods to which he was sensitive. For a time his symptoms improved. He gained 5 pounds in four months and he looked and acted better but his blood pressure continued high. In March, 1934 his headaches grew worse and he became exhausted by the slightest exertion. Since then his progress has been steadily down hill. At present emotional outbursts, insomnia, and constant restlessness have been added to the headaches and fatigability. The blood pressure is now 198 systolic and 148 diastolic. Physical examination shows nothing new. Unlike most cases of this condition there is no anemia. The urine has a specific gravity of 1.020 and contains a trace of albumin and an occasional hyaline cast.

The question which faces us in regard to this boy as in all cases of this type is, what can we do for him? Nothing in the past medical history offers an adequate explanation of the hypertension nor do any of the physical findings. Allergy seems to have no relation to hypertension.² In rare instances a tumor of the adrenal gland causes high blood pressure but this is usually paroxysmal. It has been said that chromaffin tumors give rise to the paroxysmal type while tumors of the adrenal cortex may produce a sustained hypertension. A number of cases have been recorded in the literature where surgical removal of the tumor has brought about a cure.³ A pressor

substance related physiologically to adrenalin was found by Hoyle⁴ in the blood of a boy of fourteen suffering from hypertension. There is no direct evidence that in this patient the adrenals are at fault. However, in similar cases subtotal bilateral suprarenalectomy has been advocated by DeCourcy and his associates,⁵ and x-ray treatment of the adrenals has been proposed by others. Adson and Brown⁶ have reported a definite drop in blood pressure from resection of the anterior spinal nerve roots and urge that this operation be tried in younger patients with severe progressive hypertension where nephritis is not a factor. This procedure requires a high degree of technical skill and it is too early to judge what the final results may be. Nevertheless, so hopeless is the prospect in this type of case that even the most radical measures are justified.

After taking the blood pressure in a large group of supposedly normal young people of college age, I have been struck by the number of high readings. When the pressure has been recorded repeatedly at intervals of from one to five minutes, however, it has dropped to normal in the vast majority. Probably in many cases this lability is a passing phase associated with the nervous and emotional instability of youth. Many young men have told me that they can feel their "blood pressure going up" when the cuff is being adjusted. That is, they become aware momentarily of a thumping in the precordium and a pounding in the neck or head such as is felt during excitement or strenuous exertion. In others, however, the pressure fails to subside to within normal limits even after prolonged rest, and careful study shows them to be cases of hypertension. During the past three years in 41 freshmen at the University of Pennsylvania having a constant systolic blood pressure of over 150 mm of mercury and without demonstrable kidney lesions or a history of nephritis, fluoroscopic examination showed the cardiac silhouette to be larger than predicted in 20, and in 5 there was left axis deviation of the electrocardiogram. In a number of others cardiac enlargement and preponderance of the left ventricle was found although the pressure was below 150. Very few of these stu-

dents had any symptoms of hypertension. None showed evidence of congestive heart failure.

It is unknown what significance this unusual lability of the blood pressure may have for the future of the individual. It is apparently due to an abnormally sensitive vasomotor mechanism, and is usually accompanied by other signs of sympathetic stimulation such as sweating and increased heart rate. In such persons the response to stimuli is greater than in the average, and they may be classed as hyperreactive normals. It is impossible today to say how many of them will in future years develop a persistent elevation of the blood pressure, but by following a sufficiently large number of this group an answer may some day be given. Very suggestive studies have recently been published by Hines and Brown.⁷ They have devised a test which they believe serves as an "index of the prehypertensive state." They found a positive response, that is, a significant rise in blood pressure after immersion of one arm in water at 5°-6° C. for one minute in a group of hyperreactive normals as well as in patients with definitely established hypertension. In cases of essential hypertension the magnitude of fluctuations and the mean level of the systolic and diastolic blood pressure in response to their test was depressed by rest of from one to two weeks but not of shorter periods. A significant depression was also induced by the barbiturates and to a lesser degree by bromides, while bismuth subnitrate had no effect and calcium chloride increased the response and caused a marked delay in the return of the blood pressure to the basal level.

Many writers have asserted that there must be an hereditary or constitutional factor leading to hypertension. The studies of Ayman,⁸ Allen⁹ and others support this contention. An abnormally functioning endocrine system, a hypersensitive vasomotor center, abnormally reacting sympathetic nerve endings and arteriolar tissue may all be expressions of this factor. When it is present in an individual, the stress and strain of life and toxic or infectious agents may serve as accessory or activating factors with the development of hypertension as a

consequence The ideal would be to discover the presence of a hyperreactive background through the history of high blood pressure in the family and such tests as that described above, and to begin treatment years before the clinical manifestation of hypertension This will perhaps be possible when periodic health examinations are more widely sought In members of the hyperreactive group the same treatment may be carried out as in those who have hypertension but no other symptoms Foci of infection should be periodically sought and eliminated and any underlying abnormality be corrected if feasible I do not mean that tonsillectomy and submucous resection should be done routinely Each case should be studied and treated on its own merits Adequate rest and a habit of life free from emotional stress, excitement, and excesses of all sorts should be prescribed The patient should be urged on all occasions to cultivate above all that state of mind so beautifully described by Osler in his "Equanimitas" Regular, moderate exercise, preferably out of doors, periodic vacations with complete change of scene and physical as well as mental relaxation, the cultivation of a hobby, are all helpful adjuncts to the treatment If symptoms appear, sedatives should be given to insure proper rest and relaxation In the milder cases I have found allylisopropylacetyl carbamide (sedormid) $\frac{1}{2}$ to 1 tablet, one to three times daily and at bedtime, very helpful Sometimes one of the stronger barbiturates is required, and often bromides are useful if given over a period

The next patient, Mrs B V, belongs to a group met with in the practice of every physician She is a widow, fifty-seven years of age, undersize, weighing 144 pounds, and complaining of nervousness Ten years ago she first consulted a physician because of pain and stiffness in her large joints Her systolic blood pressure at that time was found to be 170 She had shortness of breath on exertion and became easily fatigued, but had no other cardiovascular symptoms About a year later the menopause set in with irregular menses, flushes and sweats Since that time she has had dizziness chiefly on change of position, shortness of breath on the slightest exertion, palpitation often coming in attacks when she is excited or worried, and at times she has pain in the precordium and shooting pains in the left arm She is extremely nervous, sleeps poorly, lying awake worrying, often about trivial matters She has headache which is seldom severe but is present almost daily as a dull pain in the

frontal or vertical regions. Her appetite is good. Her bowels are kept regular with mineral oil and an occasional saline laxative.

She has had no period for several years, but a few months ago she had rather profuse vaginal bleeding which continued for two hours. She has had occasional epistaxis. Some weeks ago following an altercation in the family she became very much excited and had an attack of great breathlessness, palpitation and substernal oppression. I was called to see her and found her sitting propped up by pillows. She was perspiring freely. Her lips were cyanotic and she was very restless and apprehensive. The systolic blood pressure was very much elevated being too high to be read by my instrument; the diastolic pressure was 140. A venesection was done, about 600 cc. of blood being removed before the pressure fell to 190. Her dyspnea and substernal discomfort were relieved before I left and on calling to see her the following morning she met me at the door. The pressure was 210 systolic and 140 diastolic, but she felt quite well.

condiments He was advised to rest in the middle of the day and to modify his mode of life so as to avoid unnecessary activities and as far as possible worry and strain

For about a year headache was his only complaint On November 24, 1927, after an exciting day he was seized at 1 A M by an attack of precordial pain which radiated to the left shoulder, but not into the arms No physician was called, and the pain gradually disappeared after about two hours. The following morning he felt quite well and went to business as usual Since that time, however, he has suffered from frequent attacks of precordial pain Although usually induced by exertion, especially after a heavy meal, or by excitement, they have occurred while he has been at rest At times the pain radiates down the left arm as well as to the back and left shoulder When not

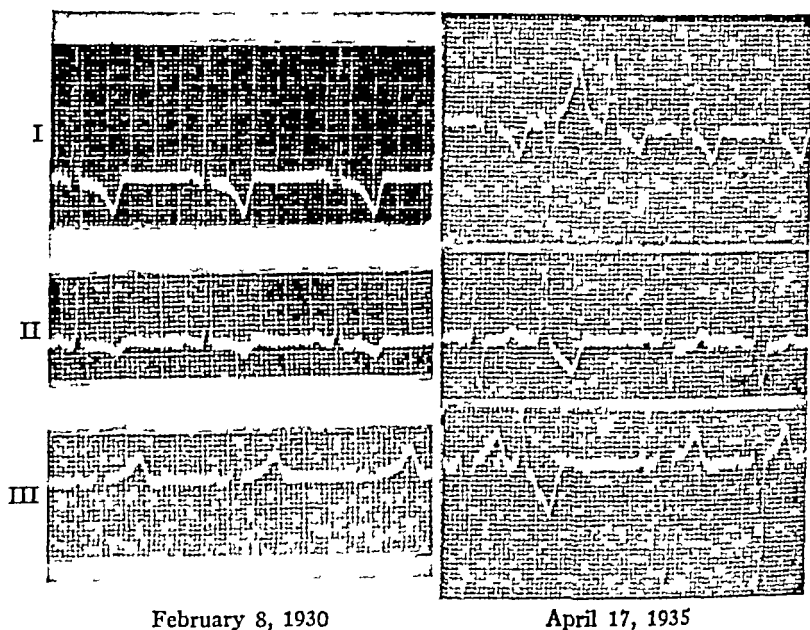


Fig 13—Electrocardiogram of Case B J

severe, it has been relieved by placing a tablet of nitroglycerin beneath the tongue or by inhaling amyl nitrite On several occasions a hypodermic of morphine has been required From time to time he has complained of pain in the calves of his legs This appears to be due to vascular spasm rather than "intermittent claudication" since the pain is not brought on by walking or other muscular exertion

In 1930, he had a peculiar seizure which, because of its short duration and the absence of subsequent symptoms, seems to have been due to a cerebral vascular crisis He fell to the floor and for about fifteen minutes was unable to move, although he did not lose consciousness A local physician was called and found the systolic blood pressure to be 235 His strength soon returned and when he walked into the office a few days later there was no sign of paralysis

He was given luminal as a sedative and added rest was prescribed. Great subjective improvement followed and he had no more episodes of this sort until February, 1931, when on awakening one morning he noticed weakness of his right upper extremity. He was unable to lift any heavy object and dropped small things like a pencil. The grip of the right hand was measurably diminished, but there were no sensory changes, no incoordination and no astereognosis. For several months some weakness persisted in the right arm and hand. This attack also may have been caused by a prolonged vascular spasm rather than thrombosis or hemorrhage.

At present he is feeling fairly well and is able to carry on a small business. He frequently has headaches but they are much less severe than those of a few years ago. There is vertigo at times but no tinnitus. He sleeps fairly well with the help of an occasional dose of bromide or phenobarbital. Although moderate exertion induces palpitation, dyspnea and precordial discomfort or

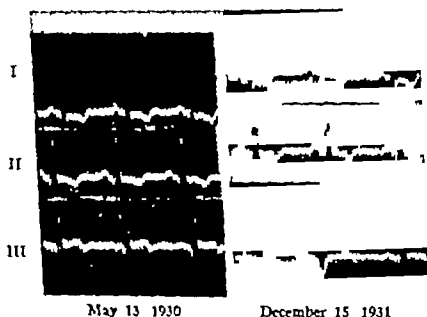


Fig 14.—Electrocardiogram of Case W. M.

pain he insists upon climbing a flight of 30 steps several times a day. From time to time he has nose bleeds which occasionally require packing. He has been becoming more stubborn, irritable and emotional often crying or flying into a rage with but little provocation. His memory is definitely falling. Nevertheless there has been no obvious change on physical examination in the past eleven years. The blood pressure has remained consistently above 200 systolic and between 92 and 110 diastolic. The pulse rate is 84 and there is an occasional ventricular premature contraction. The electrocardiogram shows evidence of marked myocardial damage. The urine has recently shown in addition to a moderate amount of albumin from 1 to 2 per cent of sugar. Eye and examination shows vascular and degenerative changes in the retina with areas of hemorrhage and exudation.

Mr. W. M. belongs to the same group of patients as the case just presented. He is a business man sixty-eight years of age who has had high blood pres-

sure for at least ten years. At that time he began to have mild precordial pain following exertion. His blood pressure ranged between 160 and 180 systolic and 80 and 96 diastolic. He had no dyspnea or palpitation, no headaches or other complaints so often seen in patients with hypertension. He had always enjoyed good health, had been a hearty eater, a hard worker and a bon vivant. He has been married twice, the second time at the age of fifty-four. When first seen in 1923, the heart was moderately enlarged and the second aortic sound somewhat accentuated, but there were no murmurs and no other significant findings on physical examination. He had no symptoms of decompensation until four years ago when he began to have moderate dyspnea and palpitation on climbing stairs and rapid walking. However, before the onset of these symptoms he usually had precordial pain, often with radiation into the left arm which made him stop and rest. At times the anginal attacks were very severe and occasionally occurred after a period of nervous strain, worry, excitement or an evening of bridge. A few attacks required hypodermics of morphine. Usually they passed off spontaneously in a few minutes.

His blood pressure gradually increased, being at times over 200 systolic and 120 diastolic. About a year ago he was awakened at midnight by a violent pain across the chest, which radiated into both arms as far as the elbow. He was given two hypodermics of morphine before the pain eased sufficiently for him to go to sleep. The systolic blood pressure was 105. Next morning he awoke feeling cheerful and comfortable. The heart sounds were scarcely audible, the rate was moderately increased with an occasional extrasystole. A diagnosis of coronary thrombosis was made from the clinical picture and he was kept flat in bed. The following morning, while having a bowel movement on the bedpan, he suddenly became intensely short of breath. He had no pain, but felt nauseated and vomited a little bile. He was extremely restless because of his labored breathing and was with the greatest difficulty restrained from getting out of bed. His face was dusky. The temporal arteries were bulging and the pulse tense. His systolic blood pressure was 222. He was bled immediately, about 500 cc being removed. Hypodermic injections of morphine, $\frac{1}{4}$ grain, and atropine, $\frac{1}{150}$ grain, were given, he inhaled amyl nitrite, and a tablet of nitroglycerin, $\frac{1}{100}$ grain, was placed beneath the tongue. Dry cupping was done over the back and in a short while his respirations became less labored, the restlessness disappeared and he soon went to sleep. His convalescence was thereafter uneventful and after six weeks in bed he was able to be up and around, feeling quite comfortable. During the past year he has enjoyed fairly good health, although he tires rather easily and continues to have precordial pain if he overexerts himself. The blood pressure today is 150 systolic and 80 diastolic. The pulse rate is 78 with frequent ventricular premature contractions. The heart sounds are feeble, the area of cardiac dullness is enlarged, the apex beat being felt an inch and a half to the left of the mid-clavicular line. There is no murmur. There are no other significant findings. As for laboratory examinations, the urine has constantly contained a little albumen and a few hyaline and finely granular casts. The blood count is normal and the blood Wassermann negative. Electrocardiograms taken from time to time have indicated grave myocardial degeneration, and suggested disease of the coronary arteries even before infarction occurred.

As I have said, the general management of patients with hypertension and the treatment of symptoms arising from the various local and general vascular crises which occur in association with it, is similar whatever the cause may be. Of course when diabetes, gout, thyrotoxicosis, or other complicating factors are present they must be taken into consideration and the treatment modified. Any remediable condition revealed by the history or physical examination should be corrected. Attention should be given not only to such physical defects as infected teeth or tonsils, chronic constipation and gallbladder disease, but any mental, psychic, or environmental conditions which might have a bearing on the case should be investigated and adjusted if possible. By gaining an understanding of the patient's frame of mind much can be done to assist him in solving his problems. Every effort should be made to quiet his fears and the thought that death lurks around the corner should be banished from his mind. Worry induced by the ill advised words of a physician or the report of an insurance examiner can raise blood pressure to alarming heights. What I have said concerning habits and the mode of life in the preorganic hypertensive state is doubly applicable to those in whom organic changes have occurred.

Rest is probably the most useful remedial measure at our disposal. Whether it be partial or for a time complete depends upon the needs of the individual patient. A half hour or an hour siesta following the noon meal or lying down for a time on returning home from the day's work is often sufficient together with a good night's sleep. In some cases a week in bed away from the cares and disturbances of daily life may be advisable, longer periods are seldom necessary. It is important, however, that the patient's mind be at ease. I well remember a case that was sent to the hospital for a rest because of hypertension and mild congestive heart failure. The intern expressed surprise that the blood pressure remained high after ten days in bed. On questioning the woman I elicited the information that she had fought against coming to the hospital.

and was greatly concerned about the welfare of her four children during her absence

The management of insomnia is often difficult. Sleep must be assured, and if bromides prove insufficient, there are many sedatives at our disposal which are fairly harmless. Chloral and the various barbiturate compounds may be tried till the one is found which best suits the individual case. The preparation and dose which induces restful sleep with a minimum of after-effect should be selected. For nervousness by day one or two doses of bromides or of one of the newer sedative preparations such as the elixir of phenobarbital, one of the other barbiturates, or a proprietary like sedobrol, may be necessary.

As for diet, no specific antihypertension régime has been devised, but there is general agreement about certain principles. Most, though by no means all, patients with hypertension are overweight. The quantity of food consumed should therefore be moderate. The evening meal especially should be light. Unless there is evidence of nephritis, and according to some authors even in its presence, meat should be allowed in moderation, that is, a small portion once daily. It has been amply proved that a daily minimum of $\frac{3}{4}$ to 1 Gm. of protein per kilo of body weight is necessary to replace that lost by the tissues through hormonal wear and tear. If albumin is excreted in the urine, the requirements are greater. It has by no means been established that meat eating is a factor in bringing about or maintaining hypertension, while the virtual absence of that condition among the Eskimos whose chief article of food is meat, is negative evidence. In patients who are overweight fats and starches should be restricted, vegetables and fruit being given to supply bulk and allay hunger. When coronary sclerosis is marked in elderly diabetics, it has been found that any great reduction of the blood sugar level brings on anginoid pain. It may be that temporary lowering of the blood sugar as the result of muscular exertion in nondiabetics with narrowed coronary vessels may account for some of the heart pain which is so prominent a symptom in such patients as

Mr B J and Mr W M Sufficient easily available carbohydrate should be allowed such patients

F M Allen has reported good results in hypertension by the use of a diet which contains virtually no salt. To be effective he insists that the sodium chloride intake must be so small that the daily excretion is not above 0.5 Gm. Not only is such a diet almost impossible to prepare outside an institution, but the results obtained by others attempting its use have not been striking. Nevertheless, it seems wise to reduce the salt intake to a minimum, while there seems no question that pepper, spices, and other condiments should be entirely forbidden. A satisfactory sample diet is the following

Allowed

A small portion of meat or fish once daily
Fruits—raw or cooked
Green vegetables.
Cereals.
Eggs in moderation—1 or 2 daily
Milk or buttermilk—2 or 3 glasses daily
Plain puddings, junket, ice cream, water ice.
Stale bread, toast.
Butter without salt
Eat sparingly especially at night.

Forbidden

Dried, salted, and pickled meat and fish
Rich foods, fried foods, etc.
Pastries, fancy dishes, etc.
Peas and beans.
Condiments.
Use salt sparingly

Although alcohol is not a direct factor in bringing about hypertension, its use should be restricted to light wines and beer among those accustomed to its use with meals, and should be let alone by others. As for tobacco, the evidence is accumulating that its effects are harmful in persons who have had cardiac pain. In others with hypertension the soothing effects of a smoke probably outweigh the harm that may result from its moderate use. Tea and coffee, because of the exciting effects of caffeine upon the central nervous system, should be

forbidden or restricted to a single cup in the morning, or one of the decaffeinized brands may be substituted

When hypertension appears in women at or shortly following the menopause, it is probably due in part at least to disturbance in the endocrine balance. Good results may often be secured by substitution therapy. Intramuscular injections of theelin, amniotin or some other potent ovarian extract often brings about a fall in blood pressure together with alleviation of the flushings, sweats, nervousness and other vascular crises characteristic of that phase of a woman's life.

One possible factor in bringing about hypertension, especially in women, is that of unsatisfied sexual desire. Very little has been said about it in the literature in relation to high blood pressure although its other psychic and nervous effects have been discussed at length. It is difficult to gather data on the subject for obvious reasons, but on theoretical grounds it would seem to be likely. One of the cases whom you have just seen, Mrs. B. V. has repeatedly told me of her sufferings in this respect following the death of her husband after a few years of married life. Another patient, a woman in her early thirties, asked me to give her some medicine to make her frigid. On inquiring I learned that following coitus interruptus she would lie awake for hours with palpitation, headache, and occasionally nausea. In a previous marriage she had had no such trouble. Instead of giving her medicine I talked with her husband and since then, I understand, the situation has been satisfactorily adjusted.

There is at present no drug which will bring about permanent reduction of the blood pressure. In many cases, especially in essential hypertension, a high level is not incompatible with well being. At times, however, particularly when such symptoms as headache, vertigo, substernal oppression, or angina are present, or when the pressure has reached such heights that there is danger of a cerebral vascular catastrophe or of cardiac failure, even a temporary lowering of the tension is a wise measure. The nitrites in adequate dosage are nearly always effective. Amyl nitrite and nitroglycerin act most

quickly, but their effect is also most transitory. They had best be reserved for an emergency such as an anginal attack. Sodium nitrite or erythrol tetranitrate act for longer periods, and when repeated several times daily are of great value.

A host of preparations have been advocated, tried, and for one reason or another abandoned. Potassium thiocyanate has been used in doses of $1\frac{1}{2}$ grain, three times daily. The results while not uniform, occasionally have been quite satisfactory. The drug is not without danger, however, and must be used with caution.¹⁰ The use of bismuth subnitrate has been disappointing,¹¹ but it appears to be harmless. Mistletoe has been widely used in continental Europe, but has not attained much popularity in this country. It seems to relieve headache, tinnitus, and dizziness in some cases when an active preparation is used such as the French *Intrait de Gui*, in dosage of 20-40 minims, three times daily.¹² Its hypotensive effects are doubtful. The iodides appear to be of some use in hypertension even when the patient is not syphilitic. One of the preparations put up in tablet or capsule form is more readily taken by the patient and is less likely to upset the stomach or produce acne than solutions of sodium or potassium iodide. Extract of watermelon seed, liver extract, and other drugs are on the market, but have not proved of value.¹³

At times, especially in cases with considerable coronary sclerosis and a failing myocardium, intravenous injections of from 10 to 20 cc of a 50 per cent solution of glucose often are followed by considerable improvement. Hypertonic glucose injected into the vein is also useful in cases where we wish to relieve cerebral congestion and elevation of intracranial tension.

The treatment of congestive heart failure is in the main unchanged by the presence of hypertension. However, when the patient has had angina the use of adrenalin is contra-indicated. Even a small dose of that drug may precipitate a dangerous or even fatal attack.¹⁴ I also wish to caution against the use of digitalis following coronary thrombosis. Clinical observations have been supported by experimental

evidence that it may do harm rather than good. It is not wise to increase the strength of the cardiac contraction before complete healing of the infarct has occurred. Furthermore, the onset of ventricular fibrillation seems to be favored in this condition by drugs of the digitalis group¹⁵

In constrictor vascular crises of the extremities, such as Raynaud's disease, which occasionally are associated with hypertension, acetyl betamethylcholine hydrochloride (mecholine, mecholyl) has been used with some success, although improvement may be only temporary. It is given by mouth in doses of from 3 to 7½ grains dissolved in water or milk. The dose is determined by the tolerance of the patient, the onset of diarrhea, flushing of the skin and tachycardia indicates that the dose should be reduced. Dry heat applied to the extremities or alternate suction and compression of the limb in an air-tight chamber may relax the spasm and improve the local circulation.

As has been pointed out by Riesman¹⁶ and others, hypertension alone is not incompatible with a long, active and useful life. Much can be done to guard the patient against catastrophe by sympathetic counsel and watchful care. When symptoms arise they may be alleviated, and often when the more serious complications such as congestive heart failure, coronary occlusion, and hemiplegia ensue, nature may be assisted in bringing the patient back for a time to the enjoyment of life.

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CLINIC OF DRS FRANCIS CLARK WOOD AND O F HEDLEY

FROM THE ROBINETTE FOUNDATION, HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA AND THE OFFICE OF HEART DISEASE INVESTIGATIONS, U S PUBLIC HEALTH SERVICE, UNIVERSITY OF PENNSYLVANIA

THE SEASONAL INCIDENCE OF ACUTE CORONARY OCCLUSION IN PHILADELPHIA

SINCE September, 1931, an intensive electrocardiographic study of acute coronary occlusion has been conducted under the auspices of the Robinette Foundation, utilizing material from various sources. These observations have been reported elsewhere¹. Between January 1, 1932, and December 31, 1934, 133 seizures were studied in 131 patients*. A review of these records has brought to light a rather striking difference in seasonal incidence. Forty seven of the attacks occurred in the three winter months, 26 in the spring, 12 in the summer and 48 in the autumn (Fig 15). Although it is well known that mortality from cardiovascular disease is higher in the colder months^{2, 4, 6} a survey of the literature has failed to reveal any reference to seasonal variations in the incidence of attacks of acute coronary occlusion. Consequently an analysis of the data has been made. We have attempted to determine whether this group of cases gives a true picture of the seasonal incidence of acute coronary occlusion in Philadelphia during the past three years.

* Two cases were studied in two distinct attacks in which the first was separated by at least five months from the second. When several painful seizures were observed in the same individual in more or less close succession only the first has been counted.

Diagnosis—The diagnosis of coronary occlusion was established in all cases beyond reasonable doubt on the basis of clinical features and electrocardiographic studies with limb and chest leads. Tracings were obtained in 122 instances during the acute stage. All but 1⁶ showed characteristic phenomena in the ventricular complex. The remaining 11 cases were seen a little later in their course but all showed evidence of recent infarction in the electrocardiogram. Twenty-four

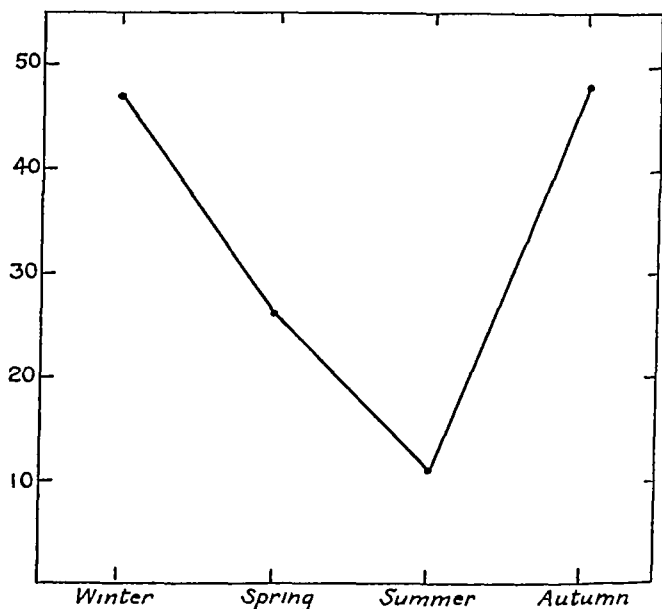


Fig 15—Distribution by seasons of 133 attacks of acute coronary occlusion occurring in Philadelphia, Pa, between January 1, 1932 and December 31, 1934, obtained from the records of the ward patients of three hospitals and from the private cases of 5 practicing physicians

came to necropsy, where pathological examination confirmed the clinical diagnosis

Method of Collecting Cases—The material consists of all the electrocardiographically substantiated cases of acute coronary occlusion which were admitted to the medical wards of three large Philadelphia hospitals during this period (90 cases). To these have been added all similarly substantiated cases seen in private practice by five Philadelphia physicians

especially interested in heart disease (43 cases) Since all available ward cases were studied electrocardiographically, this group comprises practically all the cases that occurred on the wards of these three hospitals This cannot be said of the private cases, since a much smaller proportion of them received electrocardiographic study However, there was no seasonal variation in our attempts to obtain tracings on the private patients An examination of Table 1 shows that the seasonal

TABLE 1

DISTRIBUTION BY SEASONS OF 133 ATTACKS OF ACUTE CORONARY OCCLUSION OCCURRING IN PHILADELPHIA, PA., BETWEEN JANUARY 1, 1932 AND DECEMBER 31 1934 OBTAINED FROM THE RECORDS OF THE WARD PATIENTS OF THREE HOSPITALS AND FROM THE PRIVATE CASES OF FIVE PRACTICING PHYSICIANS

Year		Winter	Spring	Summer	Fall	Total.
1932	Ward	7	5	1	10	23
	Private	3	1	2	6	12
	Total	10	6	3	16	35
1933	Ward	11	7	2	12	32
	Private	5	4	3	7	19
	Total	16	11	5	19	51
1934	Ward	17	5	3	10	35
	Private	4	4	1	3	12
	Total	21	9	4	13	47
Totals		47	26	12	48	133

incidence is approximately similar in each of the three years It is highest in the autumn and winter, lower in the spring and lowest in the summer Vacations of physicians interested in this work have probably had little effect upon the seasonal incidence The ward work went on without interruption, some

member of our group has been on duty at the heart station at each of the three hospitals throughout the entire period. Furthermore, due to the fact that most of the cases were admitted to the wards as cardiac emergencies there is no evidence that the desire for teaching material during the college session influenced the number of admissions for this condition. With regard to the private cases, the two physicians who have contributed two thirds (29) of them have not taken summer vacations of more than one week's duration since 1931. Moreover, the proportion of private to ward cases has not decreased during the summer, if anything it shows a slight increase.

Vacations of Potential Patients—It is conceivable that the lower summer incidence may be due in part to a reduction of the total population of Philadelphia during this period, rather than to a lower incidence of coronary occlusion in the population. Several points are to be considered in this connection. (1) It is probable that a greater number of private patients than ward patients take summer vacations. Thus, during this season, the percentage of private cases of coronary occlusion should decrease more than the ward cases if vacations were an important factor. Although the small number of cases renders exact figures unreliable, the opposite has taken place. (2) Fewer people leave on vacations during June than in July and August, nevertheless this month shows a lower incidence than any other. Only one case of coronary occlusion has been seen in June in three years (Table 2). (3) If the seasonal variation shown in our charts is entirely due to vacations, the incidence of acute coronary occlusion during the spring should be equal to that of the fall or winter. This has not been the case. (4) The summer incidence of coronary occlusion has been about one fourth that of autumn or winter. If vacations during this period of the year were to account for such a difference, 75 per cent of the population of Philadelphia, of the ages in which coronary occlusion is most likely to occur, would have had to leave town on June 1st of each year and remain away until September first.

Consequently it seems that (1) The method employed for

TABLE 2

DISTRIBUTION BY MONTHS OF 133 ATTACKS OF ACUTE CORONARY OCCLUSION OCCURRING IN PHILADELPHIA, PA., BETWEEN JANUARY 1 1932 AND DECEMBER 31, 1934, OBTAINED FROM THE RECORDS OF THE WARD PATIENTS OF THREE HOSPITALS AND FROM THE PRIVATE CASES OF FIVE PRACTICING PHYSICIANS

Year		Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
1932	Ward	2	2	2	0	3	1	0	0	3	4	3	3
	Private	1	1	0	0	1	0	2	0	4	0	2	1
	Total	3	3	2	0	4	1	2	0	7	4	5	4
1933	Ward	4	3	2	2	3	0	2	0	3	2	5	4
	Private	2	0	1	2	1	0	3	0	0	2	5	3
	Total	6	3	3	4	4	0	5	0	3	4	10	7
1934	Ward	8	6	2	1	2	0	0	3	1	5	4	3
	Private	2	1	1	2	1	0	0	1	2	1	0	1
	Total	10	7	3	3	3	0	0	4	3	6	4	4
Totals		19	13	8	7	11	1	7	4	13	14	19	15

collecting cases has been such as to permit us to obtain for each month and each season a representative unselected sample of the total number of cases occurring in this locality (2) Although the summer migration of people from Philadelphia may contribute to the low incidence of acute coronary occlusion during this portion of the year, it could hardly account for the marked difference shown in Tables 1 and 2. It therefore appears that the seasonal variation in the incidence of acute coronary occlusion in this group, is not attributable to obvious extraneous factors.

Discussion—The main objection to accepting these figures at their face value lies in the small number of cases in this series. We have attempted to supplement these data with information from other sources. Vital statistics from Philadelphia and from the Bureau of the Census in Washington, D. C., indicate that deaths from diseases of the coronary arteries are more numerous during the cold months. The Bureau of the Census figures for 1933 show that the curve of the seasonal incidence of death from "angina pectoris and diseases of the coronary arteries" (27,300 cases) roughly paral-

lets that of death from all types of heart disease (286,360 cases) The former curve lags slightly behind the latter in the summer months The latter lags slightly in the last four months of the year However, this information is inadequate for our purposes because (1) Acute coronary occlusion is grouped with other lesions of the coronary arteries, (2) we are interested in the *onset of the attack* whereas vital statistics only show the *date of death* Only 25 per cent of our cases died during the first three months after the attack This figure may be smaller than it should be, because a certain number of patients die shortly after the attack begins, before electrocardiographic study is possible Nevertheless, it is obvious that deaths from coronary occlusion may show a seasonal incidence that is not necessarily the same as that of onset

It must be noted that the term "spring" has been used in this paper in its ordinary sense to indicate the months of March, April and May rather than to designate the more strictly astronomical division of the year beginning with the vernal equinox This terminology has been followed in regard to the other seasons also

It may be that the incidence of thromboses of other vessels shows a seasonal variation Dana⁹ says, of cerebral vascular accidents, that "rather more cases occur in cold weather" Moreover, one sometimes wonders whether the increased winter and spring incidence of hospital admissions for peripheral arterial disease may not be due to an increased incidence of thrombosis in these vessels during the cold months However, no data have been found concerning seasonal variations in blood coagulation nor in other factors which might affect thrombosis

We have not as yet studied the relationship between daily weather changes and the incidence of coronary occlusion Moreover, we do not know whether the incidence of the disease is lower in the warmer sections of the country If so, these observations might have a therapeutic implication

Summary —(1) From January 1, 1932 to December 31,

1934 we have assembled 133 cases of acute coronary occlusion in which the diagnosis was established by electrocardiographic as well as by clinical means (2) Forty seven cases occurred in the winter, 26 in the spring, 12 in the summer and 48 in the autumn (3) The seasonal variation has been similar for each of the three years (4) The method of collecting cases has been uniform throughout the year (5) The figures may be influenced by the summer migration of people from Philadelphia However, the amount of variation has been so great that it would not seem to be explainable on that basis alone

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CLINIC OF DRS JOSEPH C DOANE AND NATHAN BLUMBERG

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OBSERVATIONS CONCERNING EMBOLISM AND THROM- BOSIS OF THE AORTA AND ITS LARGER BRANCHES

MANY of the tragedies of medicine are concerned with the sudden interruption of the blood supply to a part. Palsies of all grades, necrosis of the parenchyma of vital organs and the most dramatic deaths result when arterial occlusion by an embolus of any nature, suddenly occurs. The gradual narrowing of the lumen of an artery, however, may eventually bring about complete obstruction without death or even serious permanent disability following. Witness, for example, the discovery of a completely obliterated coronary artery at autopsy with no history of serious disability during life. The stealthy approach of arteriosclerosis with its gradual lessening of vessel caliber enables the circulatory system to accommodate itself to its local or general ischemia-producing tendencies. In the instance of arterial embolism, no time is afforded for the establishment of collateral channels which in a gradual occlusion would often take place. The sudden lodgment of an embolus in a large vessel is to be contrasted in its effects with the slow encroachment upon either the length or diameter of a vessel which is produced by an accumulating thrombus. In the first instance, sudden pain with rapidly developing loss of sensation, of normal color and of temperature results. In the latter, these changes take place more slowly and pain is of a much less intense character. It is the purpose of this presentation to discuss with illustrative cases the causes and results of obstruction, rapid or gradual, of large arterial channels and to suggest some methods of diagnosis and treatment.

The problem of coronary obstruction is of such dimensions that its discussion must be omitted from this paper. Moreover, the etiology and symptom picture of cerebral embolism and thrombosis must likewise be only lightly touched even though the frequency of embolism of brain vessels as a complication of cardiac muscular and valvular disease is well known.

The birthplace of most arterial emboli is the heart. Here, due to a great variety of muscular and valvular defects, thrombi accumulate which when dislodged are carried along arterial channels until they reach a vessel whose diameter is less than their own. Dependent, of course, on the vessel obstructed will be the symptoms produced and the degree of resulting danger to life. Embolism of the aorta itself is less frequent, perhaps because the size of these clots is generally insufficient to obstruct a vessel of this diameter. Hence, the bifurcations of large vessels are favorable points of lodgment for emboli. Thrombosis is the natural consequence of obstruction of arterial flow and the secondary symptom picture is caused by an accumulation of clot from the vessels' own blood. Complete obstruction of an artery produces prompt stagnation and coagulation of blood in its distal portion. Moreover, this thrombosing process may assume a climbing or piling-up phase which produces a series of symptom pictures as the mouths of arterial branches are successively occluded and the organs which they supply infarcted. Bull of Oslo in 1922 studied the records of 6000 patients who had come to autopsy. Thrombosis of the right heart occurred 67 times, of the left, 63 times, in both sides, 51 times. It is possible, therefore, for infarction to occur in both the pulmonary and systemic circulations simultaneously. The commonest sources of these thrombotic emboli are according to this observer, the right auricle, left ventricle, left auricle and right ventricle in the order named. In 243 cases of thrombosis, Bull reports but nine of the aorta proper. In nearly all of these 9 cases, atheromatous patches of the vessel wall were responsible for either the inception or the development of the

clot Bonowitch and Ira in 1928 studied embolism and thrombosis of the aorta and found them generally of cardiac origin. These emboli may consist of small vegetations associated with an acute endocarditis or they may consist of large clots which accumulate when circulation becomes stagnant in the auricular appendages, the apices of the ventricles or between the columnae carni. In each instance, cardiac pathology either of a degenerative or infectious nature exists. Decompensation, dilation of the cardiac chambers and various types of arrhythmia, particularly auricular fibrillation, are found when the blood thromboses within the heart. Mitral stenosis is, of course, notorious for its thrombi producing tendencies and yet no form of heart disease is exempt. It is of interest to note that mitral obstruction not only strongly predisposes to embolism throughout the whole arterial tree, but that pulmonary thrombosis is very likely to follow its stagnation producing effects on blood in the radicles of the pulmonary artery. Bacterial endocarditis, acute rheumatic endocarditis, chronic myocarditis with decompensation and more rarely aortic stenosis and regurgitation are cardiac lesions which have all been observed to be associated with the origination of arterial emboli. One would rather expect more frequent vascular obstruction from emboli than is the case when it is considered that in 15 per cent of all cases dying of heart disease, antemortem cardiac thrombi are found postmortem. In 30 per cent of mitral stenotics coming to autopsy blood clots, probably formed before death are found within the heart chamber, particularly in the left auricle and its appendages. In aortic stenosis where auricular fibrillation rarely occurs, intracardiac thrombi are sometimes found because of the accompanying enlargement of the heart.

The attention of the medical profession has been insufficiently called to the recognition of parenchymatous infarction affecting not only the brain but the spleen and particularly the kidneys. A case was recently observed by one of us in which a male of thirty-two years with mitral stenosis and a previous history of hemiplegia one year before entrance to the

hospital was incorrectly diagnosed as suffering from an acute appendiceal inflammation because of an attack of pain in the right loin. Though many red cells were found in the urine, an operation was performed but a normal appendix was removed. A later autopsy revealed a massive infarction of the right kidney by a cardiac embolus. It has been remarked that the danger to life and the production of serious permanent disability following arterial embolism depends upon the prompt formation of collateral channels before death of the part can ensue. The classical illustration of these possibilities is represented in the case of Sir Astley Cooper who ligated the external iliac and was given an opportunity eighteen years later to observe the collateral circulation resulting from the obstruction of this blood channel. Without enumerating the anatomical structures concerned in maintaining nourishment to the lower limb, it may be said that this circulation was adequately maintained throughout almost two decades.

Embolism of the aorta is a highly fatal condition. Harlow Brooks places its mortality at 90 per cent. This observer saw but 2 cases which survived canalization of the clot affording sufficient circulation to the lower extremities to prevent extensive death of tissue. In aortic embolism the floating foreign body progresses through vessels of large to those of constantly smaller diameter. In embolism arising on the venous side these emboli originate in smaller vessels and continue to traverse even wider channels until the pulmonary artery is reached where they lodge. This fact may explain the frequent difference in size respectively of emboli from these sources.

We desire to report 3 patients which illustrate some of the points brought out in the above discussion.

Case I—Pauline P., aged fifty, was seen on our service at the Jewish Hospital on October 31, 1930, presenting the following history:

One day, before admission, the patient began to experience pain in the toes of her left foot. During the previous three months, she had experienced coldness of the extremities and cramps in the calves. One year previous to admission, she had been treated for hemiplegia, probably embolic in nature. On admission, the salient points of interest pertaining to this illness were dilatation and hypertrophy of the left heart, and the left leg was cold and cyanotic.

from the ankle downward. There was absence of pulsation in the dorsalis pedis artery and of sensation to pain in the whole foot. The signs incident to the progress of the obstruction were of much interest. The mounting arterial obstruction was closely measured by oscillometric studies. The same methods were employed later in the opposite limb where a similar objective and subjective picture developed. A shower of red blood cells in the urine at the time the thrombosis reached the orifice of the left renal was noted. The temperature oscillometric and histamine readings of this patient are shown in Chart 1. The autopsy revealed about 2 inches above the bifurcation of the

CHART 1

Mrs. P. P., aged fifty

Surface Temperature Readings

Right		Left	
Foot	31.4	Foot	29.4
Leg	31.3	Leg	30.0

Oscillometric Readings

Ankle	0.25	Ankle	00
Below knee	0.4	Below knee	00
Above knee	2.0	Above knee	00

Histamine Readings

<i>Above knee</i>		<i>Above knee</i>	
wheel moderate 5 min.		none 5 min.	
flare moderate 5 min.		very slight 5 min.	
<i>Below knee</i>		<i>Below knee</i>	
wheel slight 10 min.		none some 10 min.	
flare slight 10 min.		none some 10 min.	
<i>Above ankle</i>		<i>Above ankle</i>	
wheel very slight 10 min.		wheel 0 some 10 min.	
flare very slight 10 min.		flare 0 some 10 min.	
<i>Dorsum of foot</i>		<i>Dorsum of foot</i>	
wheel slight 10 min.		wheel 0 some 10 min.	
flare slight 10 min.		flare 0 some 10 min.	

aorta a dark reddish thrombus almost occluding its lumen. This thrombus was attached to the left lateral wall a narrow channel now almost closed, running along the right side of the arterial lumen. The left renal artery was occluded and the left kidney infarcted. Both common iliacs were completely occluded.

Case II is made a part of this paper through the courtesy of Dr. F. I. Hartman of the staff of the Lankenau Hospital, Philadelphia, Pa.

Case II.—This patient Anna R. aged fifty following an attack of influenza, in which she made a satisfactory recovery began to complain of numbness and tingling in her right leg. One week before treatment was sought, both

feet became cold and anesthetic. Physical examination revealed a marked cardiac enlargement and a blowing systolic and soft diastolic murmur over the precordium. Both extremities were cyanotic and cold, necrotic in appearance, and there was an absence of femoral pulsations. A diagnosis of thrombosis of the aorta at its bifurcation was made. Autopsy revealed an enlarged and flabby heart with dilated chambers and narrowing of the mitral



Fig 16—Section of aorta showing thrombus *in situ* (Note obstruction of superior mesenteric artery and lack of total occlusion of right common iliac)

orifice. Infarction of the spleen and kidneys was present. The abdominal aorta contained a large thrombus extending downward from just below the celiac axis, the whole lumen being occluded. The renals were not involved, a lateral channel supplying blood thereto. The superior mesenteric artery was closed. The formation of the clot in this patient is demonstrated in Fig 16, showing a space between the thrombus and arterial wall allowing blood to trickle down.

Case III.—Hannah B., aged thirty five admitted to the Jewish Hospital August 6 1934 complaining of numbness and pain in the lower extremities.

CHART 2

H B aged thirty-six 8/6/34

Oscillometric Readings

Blood pressure in arm 80

Oscillometric reading at wrist 4½

Left Leg

Right Leg

Foot	0	Foot	0
Ankle	0	Ankle	0
Calf	0	Calf	0
Below knee	0	Below knee	0
Above knee	0	Above knee	0

On day of admission. Thirty six hours after apparent onset.

CHART 3

H B, aged thirty-six 8/10/34

Oscillometric Readings

Right Leg

Thigh	Below knee	Calf	Ankle
1	0	0	0
1	1	1	1
1	1	1	1
1	1	1	1

Left Leg

Thigh	Below knee	Calf	Ankle
0	0		
1	0		
	0		
0	0		

Legs much more painful. Area of dermatitis has advanced up to the knee. Left leg especially painful at the knee. Sensation still present

One week previous to admission, she had suffered a sudden attack of nausea and vomiting with tenderness over the liver area. One day prior to admission, she suddenly suffered pain in the left leg. This patient gives a history of previous cardiac symptoms. Upon examination, the patient was found to have a greatly enlarged heart in the state of auricular fibrillation with an enlarged liver. The left lower extremity was cold and cyanotic. The dorsalis pedis, the popliteal and the femoral arteries did not pulsate. She was unable to move this limb. A diagnosis of rheumatic heart disease with mitral regurgitation and stenosis, auricular fibrillation and an embolus in the left femoral artery with thrombosis was made. The result of the oscillometric, surface temperature, and histamine wheal studies is set forth in Charts 2, 3, 4 and 5. The progress

CHART 4

H B, aged thirty-six, 8/14/34

Surface Temperature Readings

	<i>Right</i>	<i>Left</i>
1 Toes	31°	29 5°
2 Foot	31 5°	29 5°
3 Ankle	31 5°	29 5°
4 Calf	31 5°	31 0°
5 Below knee	31 5°	31 5°
6 Above knee	32 5°	33 0°
7 Middle thigh	32 5°	33 5°

Gangrene is present and is much darker up to the knee. Small area on knee much darker. Area above the knee is same color.

CHART 5

H B, aged thirty six, 8/17/34

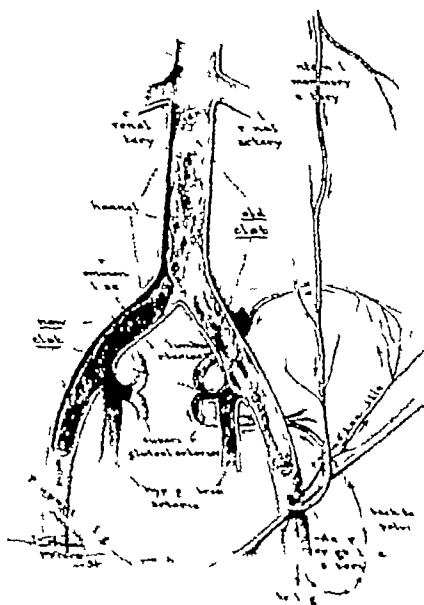
*Surface Temperature Readings**Left Leg*

Foot	29 5°
Ankle	29 5°
Calf	29 5°
Below knee	30 5°
Above knee	31 5°
Thigh	32 0°

All readings were made on the dorsum of the corresponding levels of both extremities.

of the gangrenous process is shown in Figs 17, 18. One week after admission, the patient complained of pain in the right axillary space with cough and expectoration. A diagnosis of pulmonary infarction was made. The patient died ten days after admission to the hospital. Postmortem examination revealed advanced mitral stenosis, hemorrhagic infarction of the lower lobe of the right lung, passive congestion and infarction of the lower lobe of the right lung, passive congestion and infarction of the liver and peritonitis due to mesenteric thrombosis. A large clot was present in the aorta beginning

1½ inches below the celiac axis. It was firmly attached to the vessel wall at the bifurcation. The left common iliac was completely occluded. There was a narrow channel running laterally along the right wall of the aorta connecting with the right common iliac. The right internal iliac was occluded and the right external iliac was just beginning to participate in the process. The upper



PL. 17.—Thrombosis of aorta and both common iliac arteries showing the route of collateral circulation. (Note partial occlusion of right common iliac.)

end of the process reached almost to the mouth of the superior mesenteric artery the orifice of which however was still patulous. The renal arteries were unaffected.

Some interesting lessons are to be learned from the above cases. The stealthy approach of arterial thrombosis is illus-

trated in Case I Here, a small embolus may have served as the stepping stone upon which an ascending thrombus was built Extensive vascular disease with myocardial changes were causative In Case II, no doubt thrombosis predominated over embolism In Case III, embolism originating in a dilated left auricular appendage accompanying mitral stenosis furnished the causative factor Much has been written in regard to the life-saving possibilities of embolectomy It is stated

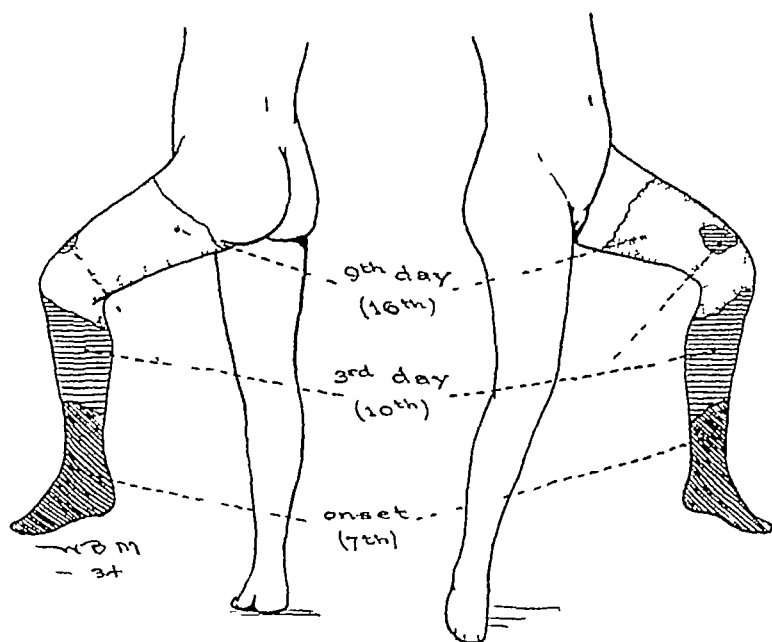


Fig 18—An illustration of the method by which gangrene extends as vessels are progressively obstructed by a thrombus

that after complete obstruction of an artery, the removal of an embolus within ten hours is likely to save a part A patient under our recent observation suddenly developed an embolus in the radial artery which was surgically removed only to have a second occurrence within a few hours Embolectomy or even amputation in any one of these cases would have been wholly futile because the source or birthplace of the clot in Case III could not be reached and because of the extensive vascular dis-

case which had already attacked the vessels of the other limb. To surgically attack an aorta occluded by an embolus originating in the cardiac chambers is possible and has been practiced not a few times, and yet to the authors, the procedure appears to offer but little since the source of the difficulty, the heart with endomyocardial disease existent or vessels with atheromatous walls, has not been remedied. Some brief observations as to possible preventive methods may not be amiss here. The danger of the dislodgment of cardiac emboli in instances where they are strongly suspected to exist is always imminent. The alteration of cardiac rhythm in the use of quinidine in the treatment of auricular fibrillation probably tends to shake loose mural or interstitial thrombi. When cardiac chambers are dilated and rapid digitalization is performed, the increase in cardiac contractility would seem likely to squeeze out or otherwise dislodge clots. Of course, the existence of cardiac thrombi can usually be but a matter of surmise. Where a septic endocarditis is present, the probability of the detachment of smaller or larger segments of the valve or its adherent necrotic tissue, or more certainly the escape into the circulation of organisms alone is always present. The injection of sera or of glucose solution into the circulation in cases of malignant endocarditis is thought to favor the breaking off of friable valve tissues. We have observed in one instance the occurrence of a cerebral embolism in the case of a graduate nurse suffering with an ulcerative endocarditis while anti-streptococcal serum was being injected into her vein. We cannot believe that the use of anticoagulants such as citric acid or the citrates can materially delay arterial thrombosis once obstruction has been definitely established. Yet, in the absence of other effective remedies, a drachm of citric acid in a glass of water by mouth or the use of the citrates intravenously should be tried. Cardiac inactivity should be encouraged when the existence of thrombi in its chambers is suspected with the hope that firm mural attachment or organization will soon delay their dislodgment. Finally the contribution which the internist may make to the surgeon in the treatment of vascular disease

is daily growing By means of refined methods in Case I and Case III, the progress of obstruction could almost be as accurately defined as would be possible by the x -ray with the presence of an arterial opaque substance The attention of the medical profession should be directed to the necessity of determining not only the exact location of the vascular obstruction, but also the method of its causation before surgical treatment is recommended

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CLINIC OF DR. HENRY DRAPER JUMP

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CHRONIC GLOMERULAR NEPHRITIS, MILD NEPHROSIS, HYPERTENSION, HEART FAILURE AND PERICARDITIS

This patient claims he was well until February 1934. At this time an accident in the factory where he worked caused a fracture of the fourth rib on the right side and indefinite injuries of his knees and elbows. He was treated in a hospital for these injuries and discharged in two weeks in "good condition." He resumed his work about April 1st but had to return to the hospital May 1st, because of crippling pains in his hands and feet. At this time a diagnosis of chronic glomerular nephritis, neuritis of the extremities, and infected tonsils was made. He had had in the years before frequent attacks of tonsillitis to which he paid little attention. There was no history of acute rheumatic fever.

His tonsils were removed in June and he recovered from this operation without undue delay or exaggeration of his ailments. He was discharged early in August and a week later had an attack of "tonsillitis." This was quickly followed by dyspnea, cough and edema of the ankles. These were somewhat relieved by a period in bed. The condition however shortly became worse and he was admitted to this hospital in September.

At this time he showed marked orthopnea, wheezing inspiration and expiration, cold cyanosed extremities, pitting edema of the hands, thighs and legs, puffiness of the face and tachycardia. There was marked engorgement with pulsation of the cervical veins, the thyroid was of normal size, pulmonary resonance was normal throughout but there were many moist râles at the bases, the heart was enlarged transversely, the pulmonic second sound was accentuated, and a harsh systolic murmur was heard in the mitral area. The blood pressure was 155/115. The liver was felt two fingerbreadths below the costal margin, but no fluid was detected in the abdomen.

The urine with an output of 180 cc (12½ ounces) and an intake of 1320 cc (44 ounces) showed specific gravity 1.010, a heavy cloud of albumin, red blood cells, many epithelial cells but no casts. The examination of the blood revealed hemoglobin 60 per cent, red blood cells 2,000,000, white blood corpuscles 120, polymorphous cells 34 per cent, lymphocytes 60 per cent, blood urea nitrogen 6 mg. (normal 12 to 15 mg.), sugar 116 mg. (normal 90 to 120 mg.), total protein 6.75 Gm. (normal 6 to 8 Gm.), albumin 2.76 Gm. (normal 4.6 to 6 Gm.), globulin 3.99 Gm. (normal 1.2 to 3 Gm.), cholesterol 216 mg. (normal 15 to 250 mg.). The McManis concentration test showed a variation in specific gravity 1.011 to 1.014 (normal variation 9 points) with a larger amount by

night than by day. The phenolphthalein test gave 32 per cent excretion in two hours and ten minutes (normal 50 per cent).

With rest in bed and the use of digitalis he improved considerably. Two weeks later another sore throat came on with a marked increase in temperature, pulse, and respiration, and a leukocyte count of 25,000. It was accompanied by edema of the larynx, swelling and tenderness of the thyroid gland and marked swelling of the veins of the neck. A diagnosis of acute thyroiditis was made. This all subsided within a week but the infection took its toll from his heart and kidneys. The edema, cyanosis and dyspnea returned, the urinary output was lowered and a small amount of fluid appeared in the right chest. Blood urea nitrogen went to 68 mg. A few days ago a precordial pain with a pericardial friction appeared, but as yet no exudate of fluid into the sac has been detected. That is the condition as you see him today.

The diagnosis of *nephritis* is made on the swelling of the hands and face, anemia, low output of urine, increased percentage of the night urine, with albumin, red blood cells, and epithelial cells in it, nitrogen retention, decreased phenol-sulphonphthalein excretion, and decreased ability to concentrate the urine. This is probably the primary disorder and it is believed that the repeated attacks of sore throat have been the cause.

Nephrosis is diagnosed because of the marked albuminuria, a blood chemistry which shows a reversal of the amounts of albumin and globulin, decrease of total protein, and a moderate increase of cholesterol. The low urine output, albuminuria, and marked edema may be accounted for by the associated kidney and heart disease.

The diagnosis of *heart failure* is warranted by the marked dyspnea and cyanosis, extensive dependent edema with oliguria, tachycardia, enlarged heart with mitral regurgitation, and venous stasis, with consequent congestion of the lungs and enlargement of the liver.

The history of the patient's disease may be quite clearly outlined. For years he has had attacks of tonsillitis. The acute infections, and particularly those of the tonsils, appear to be the chief causes of glomerular nephritis. There probably never was in him a frank, acute nephritis with outstanding symptoms, but an insidious inflammation and destruction of glomeruli. Each attack added a bit more trouble and this was

intensified by the patient's neglect of the infection. If progress is to be made in checking the incidence of nephritis, which is one of the chief causes of death, the people must be trained to take better care of mild infections. Blood pressure increased as kidney damage increased. In glomerular nephritis, the tubules degenerate in proportion to the inflammation of the glomeruli. As the tubules degenerate, nephrosis develops with changes in the blood cholesterol, total protein, albumin and globulin. If the acute nephritis recovers, the tubular degeneration may continue and there remains an unmixed nephrosis. On the other hand the glomerular damage may predominate and the tubular play only a minor part. This is probably the case in this man, for his nephrosis is not severe the important consideration being the decrease of albumin and increase of globulin. The nephritis and the moderate mild nephrosis are not enough to account for his marked dyspnea, edema and albuminuria.

We must then look to his heart disease and heart failure to explain these. The mitral insufficiency may have been caused by tonsillitis or an unrecorded attack of rheumatism. More likely it is a result of his hypertension and arteriosclerosis. The murmur in such cases is harsh, as his is. The myocardium fails as nephritis and hypertension increase. Each attack of tonsillitis has added to this damage. He had edema of his ankles after a sore throat last August. He improved until another attack of tonsillitis occurred after his admission to this hospital. This was followed by thyroiditis with edema of the glottis and this combination apparently did great damage to heart and kidneys. While removal of faucial tonsils does rid the throat of most of the lymphoid tissue and prevent further attacks there is always left some of this tissue. This may become inflamed and cause much disturbance. Apparently that was the case here. Kidney failure is progressing as is evidenced by his increasing blood urea nitrogen. Then two days ago pericarditis appeared. This is probably an expression of his uremia.

In planning his treatment we are confronted with heart and

kidney failure The most important thing beside complete rest in bed is *digitalization* This was done before the last infection and with the slowing of his heart the urine increased and edema lessened But his myocardium is probably less responsive now Then for the first twenty-four hours let us give him a drachm (4 cc) of tincture of *digitalis* every six hours, for the next day 30 minims every four hours while he is awake This should be continued until his pulse reaches 66 to 70 If this be taken just before each dose of *digitalis*, the drug may be omitted when it reaches 70, and toxic effects avoided

Liquid intake should be restricted to 2 to 2½ pints (1000 to 1250 cc) When an increased output is established and edema is subsiding this may be cautiously increased if the output keeps pace with the increase *Salt* must be restricted for practical purposes, it may be withheld in cooking and an after dinner coffee spoonful given with each meal This amount sprinkled over the food pleases the patient more than an equal quantity mixed with the food The *Karell diet*, a glassful of milk at 8, 12, 4, and 8 o'clock, would be of value at the beginning It is low in salt, protein, and liquid, it contains but 27 Gm of protein and less than 600 calories This cannot be kept up for more than three or four days because of its low nutritive value and the discontent of the patient

If digitalization does not increase the output considerably *diuretics* are called for They are of little value in edema of nephritic origin, but of considerable value in that due to heart failure The insufficiency of the heart in this patient is probably responsible for most of his edema The powerful new *mercurial diuretics*—novasural, salyrgan and mercupurin—cannot be used except with great caution, because they may increase the kidney damage Ammonium chloride or ammonium nitrate given for two days before will increase their action The dose 10 to 15 grains (0.6 to 1 Gm) is given six to ten times a day The drugs are furnished in 10 per cent solution in ampules and 1 to 2 cc are given intravenously or intramuscularly every three or four days If red blood cells increase in the urine or the output decreases, they should be stopped

The *purin derivatives* Theophylline (theocin), theobromine and caffeine are effective. Their diuretic value is in the order just mentioned. The dose of the *theophylline* is 15 grains (1 Gm) a day divided into 3 to 5 doses. It is prone to cause nausea and seems not to be effective after three or four days. *Theobromine* has usually been more effective in my hands than theobromine sodiosalicylate (diuretin). Either should be given in 15 grain (1 Gm) doses three or four times a day. *Caffeine* is given in the same dose as theophylline. The cerebral excitement which it causes is a detriment to its use in some cases. The alkaline diuretics are usually not so valuable as those just mentioned.

The edema of the legs is often slow to move and bursting of the skin may occur. The *Southey tubes*, one in each of the inner and outer sides of the thighs and legs (8 in all) will take out a great deal of the contained fluid. *Puncture* into the subcutaneous tissues will do the same, but the constant oozing will keep dressings and bedclothes wet. Infection may follow either of these measures, particularly when nephrosis is present. This danger, however, has been exaggerated, for it seldom occurs if antiseptic dressings are applied. The small amount of liquid in the pleura and pericardium may be ignored for the present, for it will probably be taken up as the heart action improves. In case it increases and embarrasses the lungs and heart, it must be aspirated.

In planning the *diet*, the large percentage of albumin excreted would impel us to feed more protein to make up for the loss. But the quantity of urine is low and the total loss is not much. The total blood protein is about the normal. If it be true that edema occurs in nephrosis, when this falls below 5.5 Gm per 100 cc, we cannot credit his edema to this cause. The high urea nitrogen in his blood does call for a low protein diet and I would give him 45 Gm a day, which is more than $\frac{1}{2}$ Gm per kilo of body weight. I believe the retained nitrogen will decrease as the quantity of urine increases and then we can increase his protein gradually to 1 Gm per kilo. This higher amount will be of value in improving his nutrition and

blood value While he is on the low protein diet an increased amount of carbohydrates should be given to furnish energy and save his body proteins This can be accomplished by giving fruit juices, bread and potato, and adding lactose to the milk

But the outlook is bad The long-continued hypertension and frequent infections have probably so hurt his myocardium that it will never become very effective If, however, it does respond, I believe his nephritis will be less evident or will be more amenable to treatment The removal of the tags of tonsils and other lymphoid tissue by the electric needle or cautery, may be considered when his condition warrants it But it is a question whether such a time will arrive

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PROTEOSURIA IN AMYLOID NEPHROSIS

A CASE of amyloid nephrosis is presented in order to report certain interesting findings in the urine. The history and physical findings may be briefly summarized as follows:

History.—The onset of the patient's disease began at the age of eleven years when he was hit below the right knee with a baseball. Within a few days after the accident in April 1924, he was operated upon for an acute osteomyelitis of the right tibia. A sequestrum was removed from the right tibia in June 1924. His convalescence was prolonged and pus drained from the lesion in the right tibia for over a year. In July 1926 an osteomyelitis of the right ilium developed and in April 1927, an osteomyelitis of the left humerus from which a sequestrum was removed. In August 1930 the right leg was amputated because of the chronic osteomyelitis. At this time there was a discharging sinus at the right elbow. Until April 1932, the patient apparently presented no evidence of kidney disease. At this time however, his urine began to show albumin, hyaline and granular casts, and his left leg became slightly edematous. The patient was referred to the medical ward and was observed for several weeks in all during the course of 4 admissions to the hospital from April 1932 until the time of his death in February 1934.

Clinical Course and Physical Findings.—On admission to the ward in April 1932 the patient had no complaints except of swelling of his left leg and occasional headache. He weighed 80 pounds and appeared sparsely nourished, poorly developed and pale. He was an Italian youth looking at least five years younger than his given age of nineteen years. He had a generalized astasia. The osteomyelitic lesions were entirely inactive. The heart was slightly enlarged with a systolic murmur heard at the apex. The liver and spleen were palpable. The urine contained large amounts of protein, many hyaline and granular casts and showed a tendency to fixation of the specific gravity between 1.008 and 1.01. Doubly refractile bodies were found in the urine. The average of the erythrocyte counts was 3,600,000 per cubic millimeter and there was a persistent leukocytosis between 14,000 and 16,000. The

several days the patient developed anuria, hiccoughs, and became semicomatose and died of uremia.

Necropsy Findings.—The pathological diagnoses included amyloid disease of the kidneys, spleen and adrenals, myocardial hypertrophy, early pericarditis and peritonitis, pulmonary tuberculosis.

The kidneys of approximately normal size were slightly granular with marked reduction of the cortex and enlargement of the pyramids. Microscopically almost all of glomeruli were extensively infiltrated with amyloid (Fig. 22). These infiltrations seemed to arise in the walls of the vessels and to compress glomerular spaces so that the tufts often lay in contact with the capsule walls. There was in addition considerable round cell infiltration. Extensive amyloid was present throughout the pulp of the spleen and in the cortical zone of the adrenals. No amyloid was found in the liver.

The lungs contained a few old tubercles and one small tubercle was seen in the liver. The heart was enlarged and sparsely covered with a fibrinous rind. A slight amount of exudate in the peritoneum bound loops of the small intestine in a few places, however none of these adhesions were old.

Laboratory Studies.—On Fig. 19 are given the mean systolic and diastolic blood pressure readings, the urea clearance and phenolsulphonethalein tests, urea, nonprotein nitrogen and the serum protein concentrations during the period of observation. It will be seen that there was a diminution in the concentration of protein, particularly the albumin fraction during the early period of observation when he had much edema. The concentration of albumin remained below the normal level throughout the entire period of study.

The concentration of blood urea nitrogen and nonprotein nitrogen increased steadily throughout the course of his illness, the concentration of the urea nitrogen being 165 mg. per 100 ml. on the day before death. The concentration of creatinine in the blood at this time was 14 mg. per 100 ml.

The urea clearance was gradually diminished to 11 per cent of average normal function prior to death. In estimating the urea clearance no correction was introduced for diminution of tissue resulting from the amputation of the leg.

In November and December 1932 a Congo red test was made and special studies were carried out with respect to the electrolyte pattern of the serum and the protein excretion in the urine.

Congo Red Test.—Bernhardt¹ has shown that in normal individuals approximately 0 per cent of Congo red injected intravenously disappears from the blood stream within one hour after the injection, whereas, there is 40 to 100 per cent disappearance in patient with amyloidosis. Three and one-half cc. of a 1 per cent solution of the dye injected intravenously completely disappeared from the blood stream at the end of one hour and none was recovered in the urine.

Serum Electrolytes. The concentrations of serum electrolytes are given in the Table below. It will be seen that the concentrations of phosphate and chloride were increased. In view of the decreased concentration of protein and the normal concentration of total base, it is apparent that the increased concentration of chloride is compensated for the decreased concentration of base.

TABULATION

Serum Electrolytes November 14, 1932

Total base	144.0 m. Eq. per liter
Serum sodium	136.4 m. Eq. per liter
Serum calcium	4.9 m. Eq. per liter
Serum magnesium	2.0 m. Eq. per liter
Serum chloride	108.8 m. Eq. per liter
Serum inorganic phosphate	5.5 mg. per 100 ml.
Serum CO ₂	50.0 volumes per cent
Serum protein	4.0 Gm. per 100 ml.
Serum specific conductivity	0.01280 mhos

Urine Proteins—The results of the studies as to the nature of the protein excretion in the urine may be summarized by the three fractionations given in Fig. 20.

Fractionation I—The filtered alkaline urine was carefully neutralized and heated to 100° C. in a water bath. A precipitate formed which could be either albumin, globulin, or both. The filtrate gave a strong Biuret reaction indicating the presence of primary or deuteroproteoses or peptones.

To this filtrate was added (NH₄)₂SO₄ to half saturation. A precipitate of primary proteose was obtained. This filtrate gave a Biuret reaction indicating the presence of deuteroproteose or peptone.

To this filtrate was added (NH₄)₂SO₄ to complete saturation. A heavy precipitate of deuteroproteose was obtained. The filtrate from this fraction gave a faint Biuret reaction indicating the presence of small amounts of peptones.

Fractionation II—To filtered neutralized urine (NH₄)₂SO₄ was added to half saturation. A heavy precipitate developed which could be either globulin or primary proteose. When water was added to this precipitate a clear solution was obtained. Sufficient salt adheres to such a precipitate so that globulin if present goes into the solution. However, globulin is coagulable by heat and proteose is not. When this solution was heated to 100° C. no precipitate developed, indicating that the precipitate consisted of primary proteose and not globulin.

The qualitative analysis of the proteins in the urine thus indicated the presence of albumin, primary and deuteroproteose and traces of peptone.

Fractionation III—For the quantitative estimation of the proteoses present, Hahn's method as developed by Seibert² was used. In this method 16 per cent trichloroacetic acid and 4 per cent phosphotungstic acid are selected as the precipitants which will differentiate most sharply between the protein molecule and its fragments—the proteoses. Trichloroacetic acid precipitates albumin and globulin whereas, phosphotungstic acid precipitates albumin, globulin, and proteoses. The quantitative analyses of the urine indicated that as much as 17 per cent of the total nitrogen present was proteose nitrogen and that the urine contained in one day's excretion as much as 2.4 Gm. of proteose nitrogen.

Of further interest was the behavior of this urine with respect to heat. When the acidified urine was heated in a water bath to 100° C. albumin was obviously precipitated. When this precipitate was filtered off while still hot,

FRACTIONATION OF URINE	100% H ₂ O	100% K ₂ SO ₄	100% NH ₄ SO ₄	100% K ₂ SO ₄	100% NH ₄ SO ₄	100% H ₂ O	100% K ₂ SO ₄	100% NH ₄ SO ₄
Albumin	100%	100%	100%	100%	100%	100%	100%	100%
Globulin	100%	100%	100%	100%	100%	100%	100%	100%
Primary Proteose	100%	100%	100%	100%	100%	100%	100%	100%
Deutero Proteose	100%	100%	100%	100%	100%	100%	100%	100%
Peptone and Nonprotein N	100%	100%	100%	100%	100%	100%	100%	100%

Fig. 0—Protein excretion in the urine

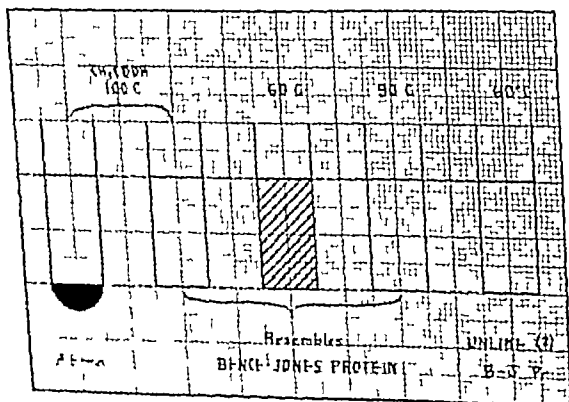


Fig. 1—Behavior of the urine with respect to heat

which was obtained until the temperature was decreased to approximately 30 C. at which point a precipitate appeared. Upon further heating this precipitate dissolved and thus behaved like Lane Jones protein. However

after one or two recoolings the precipitate did not reappear and thus was probably unlike typical Bence-Jones protein. This phenomenon is represented graphically in Fig. 21.

DISCUSSION

Bence-Jones,³ in 1847, described the behavior of urine from a case of osteomalacia. The protein of this urine was not precipitated with nitric acid in the cold except on long standing but when the urine was heated and allowed to cool it became solid. This precipitate redissolved on heating and formed again on cooling. Urines responding in this way have been found in a variety of clinical conditions such as multiple myeloma, diseases of the bone marrow, leukemia, Hodgkin's disease, hypothyroidism, etc. No one, in spite of numerous attempts, has succeeded in isolating consistently from such urines a protein of uniform characteristics. The isolated proteins have varied in their capacity for crystallization, in their crystal forms, in amino nitrogen content, and immunologically. No one has clearly defined what constitutes a Bence-Jones protein and no one can state whether there is one such protein the properties of which vary because of the associated proteins and other conditions or whether there are several such proteins. The substances of this class studied by various workers have often been classified as proteoses, but by some writers have been regarded as more nearly akin to the simple proteins.

In the urine we have studied we prefer merely to report the finding of albumin and of primary and deuteroproteose and a behavior with respect to heat which resembles, through the period of one or two coolings and reheatings, Bence-Jones protein, but without asserting or denying that we have present a protein of the Bence-Jones type.

Of greater interest is the fact that many observers have reported large quantities of globulin in the urine of patients suffering with amyloid nephrosis. In the reports that we have examined there apparently was no attempt made to distinguish between a globulinuria and a proteosuria. The findings in our case of proteoses and of no globulin suggest to us the possi-

bility that proteosuria rather than globulinuria may be a characteristic finding of amyloid nephrosis

The Congo red test has, in recent years, been shown to be an important aid in the clinical differentiation of the lipid and



Fig. 11.—Photomicrograph. Histological section of kidney showing the amyloid infiltration

amyloid types of the nephrotic syndrome. Previously, the differentiation usually rested upon a consideration of the history. When an infectious process of long duration and

dated the appearance of nephrotic symptoms in patients with the physical findings of enlargement of the liver and spleen, amyloid nephrosis was generally suspected. With the use of the Congo red test more direct evidence as to the presence of amyloid material may be obtained. The principle of the test depends upon the fact that amyloid material absorbs Congo red, causing its rapid disappearance from the blood stream and a diminution in its recovery in the urine. The value of this test, first described by Bennhold in 1923, has been amply demonstrated by many investigators.

SUMMARY

Studies of the protein excretion in the urine and the electrolyte pattern in the serum of a patient with amyloidosis are presented.

The urine contained large amounts of primary and deuteroproteoses, and albumin. It exhibited a behavior with respect to heat which somewhat resembled Bence-Jones protein.

The diminution in the concentration of base bound by protein in the serum was compensated for by the increase in the concentrations of chloride and phosphate.

The Congo red test in this case was typical for amyloidosis.

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CLINIC OF DRS ELDRIDGE L ELIASON AND JULIAN JOHNSON

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DIAGNOSIS OF ATYPICAL ACUTE APPENDICITIS

APPENDICITIS, acute in type, is a very common disease. It is reported to be the cause of 75 per cent of acute inflammatory processes in the peritoneal cavity of the adult and 90 per cent of similar conditions in children under ten years of age. The condition has been pathologically recognized since the eighteenth century and clinically known since the nineteenth century. Despite these many years of familiarity the mortality is entirely too high. It would seem that a disease with such a simple orderly and typical symptomatology as described in the textbook should be recognized. Such cases are properly diagnosed early and mortality figures in these instances are commendable as they should be. But atypical cases occur all too frequently. Royster quotes "the only hand that paints a perfect pathological picture is the hand of death."

Livingstone, years ago, reported the frequency of the classical or typical signs and symptoms in acute appendicitis cases under his care to be as follows: Typical pain 75 per cent, nausea or vomiting 70 per cent, localized rigidity 59 per cent, temperature rise 67 per cent, leukocytosis 76 per cent.

In our experience the above figures are somewhat approximated showing right lower quadrant symptoms in 77 per cent, nausea and vomiting in 68.2 per cent, local rigidity in 79.6 per cent, temperature rise above 99° F. in 71 per cent, leukocytosis above 10,000 in 82 per cent. It will be seen on combining these two groups of figures that about 25 per cent of cases are atypical in that one or more of the so-called 'cardinal findings

of acute appendicitis are absent. It must be understood that pain is the *one* and only symptom that every case of acute appendicitis has. It, however, may be atypical in localization, its character, its duration and severity.

For future comparison it will be well to outline here the clinical findings in the typical case. In such there is a very definite sequence and orderliness.

Primary Pain—Pain of a colicky or cramplike nature with more or less general distribution over the abdomen begins at any time regardless of ingestion or activity, rather suddenly and continues with increased severity in intermittent waves, often described as gas pains. At this period there is no localization, no rigidity and no tenderness. This pain reaches its maximum in the first four to five hours (Bernie) and is complained of in the epigastrium or around the umbilicus.

Primary Nausea and Vomiting—These follow, never precede, the primary pain, within an hour or two and continue for a short time only. Excessive and long-continued vomiting is not usual, as in gallstone colic for example.

Secondary Pain, Tenderness and Rigidity—At this time, four to six hours after the onset of the disease, the pain, now more or less constant, with exacerbations, becomes localized in the right lower quadrant (McBurney's point) and is associated with local tenderness and muscular rigidity. The vomiting now has ceased. Shortly after the pain (two to six hours) there is some rise of temperature, usually around 100° F. The pulse rate is somewhat increased and there is an increase in the polymorphonuclear leukocytes. There is a tendency to constipation and the patient is uneasy and restless. Any case that deviates from the above is more or less atypical and consequently on the average more difficult to diagnose promptly. Although several other factors, such as delay due to other insurmountable conditions, anesthesia accidents and surgical blunders may account for some mortality, yet analyses of our case reports indicate the chief cause of the high mortality is the delay in making the proper diagnosis until after the disease has ceased to be limited to the appendix. The

absence of the typical symptoms may be considered for the purpose of study from the standpoint of age. In literature the statement has been often made that acute appendicitis is chiefly a disease of youth and young adults, and until more recently only infrequent reference was made to cases occurring in children under five years and adults over sixty years of age. Latterly authors are stressing the occurrence of these two groups and reports indicate about 15 per cent of cases occur in the first decade of life. Perusal of our cases shows that the youngest was three and one-half months old, 27 per cent were five years of age and 94 per cent were under ten years. The delay in diagnosis is clearly shown by the fact that 94.1 per cent of cases under five years of age had to have drainage and 100 per cent of adults fifty five years or older had the wound drained. Maes found the same condition in his older patients. Bearing in mind that appendicitis is responsible for from 75 to 90 per cent of acute intraperitoneal infections regardless of age, will reduce the number of delayed diagnoses. In other words, be "appendicitis minded" until you are convinced otherwise. A young child with a resentful abdominal wall and who is wakeful requires careful observation. Children with the referred abdominal signs of other febrile disturbances will usually sleep. Persistent vomiting, even in the absence of other symptoms should make one suspect appendicitis until proved otherwise. In children as in adults, appendicitis may follow acute tonsillitis, bronchitis and may be concomitant with pneumonia. One such case with the double diagnosis made preoperatively occurred on the writers' service. Chills in appendicitis and preceding diarrhea occur more often in children. Confusion with pneumonia is frequent. Adams and Berger reports in 145 cases of pneumonia, 17.5 per cent were incorrectly diagnosed appendicitis. The history of a "cold," severe chill, respiratory hurry, a grunt, mobile, nasal alae, diarrhea, high fever, 103° to 104° F. facial flush and sometimes labial herpes point the way. Children with respiratory condition are usually restless and irritable.

Appendicitis does occur simultaneously with the exanthem

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Speese and Klein called attention to acute mesenteric lymphadenitis as simulating acute appendicitis most closely If confusion exists it is best to operate for appendicitis as the operation does no harm to the lymphadenitis present

The writers have had this experience several times In one child in particular who had persisting vomiting, colicky pain, audible peristalsis, generalized abdominal tenderness and right lower quadrant resistance, associated with 22,000 leukocytes, a normal appendix was found, also a diffuse mesenteric lymphadenitis One node removed for culture showed Streptococcus hemolyticus The patient recovered nicely

Pneumococcic peritonitis simulates appendicitis but it is characterized by a much higher temperature, 104° to 105° F, diarrhea, leukocytosis of 40,000 to 50,000, occurs usually in girls and frequently has an association with pulmonary, ear, or pharyngeal infection This condition, as well as pneumonia, measles, scarlet fever do poorly if operated upon under a diagnosis of appendicitis

Pyelitis, acidosis, mesenteric lymphadenitis, parietal neuralgia, gastro-enteritis, are not endangered greatly by an appendectomy When in doubt it is safer to operate

Gaining the child's confidence before touching it, then directing its attention and your examination to the unsuspected areas first will often permit a later approach to the spot under suspicion Many times the child if asked will indicate with his own finger the spot of tenderness or pain

Persisting colicky pain, *followed* by nausea or vomiting with local or general resentfulness, tenderness and rigidity is strongly suggestive of appendicitis in the child Under such circumstances it is best to remove the appendix You may remove some normal appendices but you will save many lives also

Case I.—An infant three and one-half months old was admitted to the hospital with the history that a right inguinal hernia had been down for two days. The child had been vomiting and had no bowel movement. Physical examination disclosed a greatly distended abdomen, with absent peristalsis. The hernia was neither tense nor tender and yet the child was desperately ill and almost moribund. Under local anesthesia the hernial sac was opened and normal gut exposed. The sac contained a gangrenous appendix. Appendectomy and herniorrhaphy was performed and the patient recovered.

Case II.—A little girl, four years old while recovering from tonsillitis, developed generalized abdominal pain at 11 o'clock. Five hours later the temperature was 102° F., the leukocyte count 18,000. At this time the entire lower abdominal wall was rigid. Laparotomy revealed acute suppurative appendicitis the pelvis being full of a cloudy fluid.

Many children have attacks of acidosis with associated pain, temperature and vomiting. This same picture may readily be secondary to acute appendicitis. If in doubt, treat the patient for both conditions, even though you are positive of acidosis and uncertain of appendicitis, as operation properly guarded will not jeopardize life and often cures the cyclic vomiting attacks of acidosis. All writers agree that the mortality in children under five years is two to three times higher than in adults. Diagnostic difficulties are directly responsible. In view of the fact that the patient is often too young to accurately describe the pain, the most constant cardinal symptom, the diagnosis is made most difficult. Great tact, patience and psychology help in this situation—otherwise an accurate physical examination will be impossible.

At the other extreme of life also the diagnosis is often difficult. The abdominal wall of the elderly is frequently flabby with loss of muscle tone and no semblance of rigidity. Old people do not have the same acute reaction to pain as young adults, nor do they vomit as readily, nor are they always very lucid and accurate in their description of the course of the disease. The multiplicity of other diseases of the aged makes for greater confusion and uncertainty of diagnosis. Many of these patients have abdominal scars of previous operations, the nature of which is often unknown, as to whether the appendix was or was not removed.

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Many writers report that in their experience the appendix is found in the pelvis in from 25 to 30 per cent of their cases. In this position the appendix gives little or no right quadrant findings, the pain and even the tenderness on palpation is referred to the epigastrium—hence the all too frequent diagnosis of indigestion.

In our experience the diseased appendix lying in the pelvis most often gives epigastric pain and rectal tenderness with some tenderness over and rigidity of the extreme lower end of the right rectus abdominis muscle. Pressure over this area frequently gives pain in the epigastrium. As stated only 44.7 per cent of our cases had tenderness or rigidity at McBurney's point whereas 31 per cent had rectal pain and tenderness. Further these pelvic cases had an incidence of 16.9 per cent with epigastric pain, and rectal tenderness in 57 per cent of cases. Pain and tenderness in the left pelvis invariably means either a pelvic abscess or peritonitis. It must be remembered that "secondary pain" and tenderness and rigidity are present at the site of the diseased appendix, i. e., a retrocolic appendix gives loin pain and tenderness, a left sided appendix gives corresponding findings, a pelvic appendix gives rectal tenderness. The diseased appendix refers its peritoneal pain manifestation to the nearest peritoneal surface, right or left, anterior or posterior high or low, as the case may be, and not by any means always at McBurney's point or even in the right or lower quadrant.

At operation in 30.2 per cent of our cases the appendix was found in the pelvis.

The existence of abdominal rigidity varies enormously depending upon the position of the diseased appendix. About one fifth of all cases have no rigidity mentioned in reports. When the appendix lay to the left of the cecum and tucked

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The question to be answered here as always first, is the case surgical, second, should it be operated upon at once or delayed and third, what is the actual diagnosis

At all ages with the peritoneum under real suspicion, early operation will save lives

Atypical Character of Pain—There is slight variation in the primary pain. It is almost always generalized colicky, beginning in the epigastrium or around the umbilicus. From here on, however, variations are numerous. It may require from four to twenty-four hours for it to localize or it may not persist in epigastrium throughout. It may be severe in degree. It bears no relation to the pathological changes in the appendix until gangrene has occurred. The most severe colics may be due merely to an obstruction by a fecolith which may promptly dislodge with sudden cessation of pain. On the other hand, many times serious inflammatory changes and even sloughing is heralded by extremely mild pain. The patient's threshold of pain varies greatly. The stoic may confuse the proper interpretation. A hospital intern once remarked that he had a mighty hard time not flinching when the surgeon palpated his tender McBurney's. The hypersensitive nervous apprehensive patient will complain bitterly and out of all proportion to the other findings.

As the general character of the pain ceases it localizes and becomes more nearly constant and is dull, aching in type. It is now bearable and exists as a soreness. Abrupt relief of pain may mean subsidence of the disease if all other findings ameliorate simultaneously. Otherwise, it means the onset of gangrene and he is worse rather than better.

McBurney's Point Symptoms—Many of the cases of delayed or erroneous diagnosis are due to the fact that too much importance has been attributed to pain, tenderness and rigidity at this historical point. As mentioned earlier in this discussion, Livingstone found atypical pain and tenderness at this location in only 75 per cent of his cases. The writers found absolute McBurney's point symptoms in only 44.7 per cent of cases although 77 per cent had symptoms of pain and of

tenderness in the right lower quadrant. In other words in 1 out of every 4 cases the local pain symptoms taught as indicative of appendicitis are not present. Rather should it not be taught that the pain manifestations of tenderness and rigidity localize over the appendix wherever it may be.

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under the ileum just over the brim of the pelvis in what we term "the swallow nest" position, rigidity was absent in 34.2 per cent of cases

Superficial tenderness, parietal hyperesthesia may or may not exist regardless of the position of the appendix which has often led to erroneous or delayed diagnosis. Livingstone limits the hyperesthesia of appendicitis to the triangle between umbilicus, pubis and anterior superior spine. Maximal hyperesthesia posteriorly is regarded as not due to appendicitis. It is certainly true, however, that acute appendicitis can be associated with a widespread so-called "intercostal" or "parietal neuralgia" as manifested in the following case

Case III.—Patient, a physician, gave the history of generalized "gas" pains of twelve hours' duration at which time the pains became much less and persisted only as a sense of gaseous fulness. Temperature at this time was 99.1° F, pulse 86, leukocyte count 19,000. There was no rigidity of the right oblique muscles but there was a resistance of the lower 3 inches of the right rectus abdominis muscle. There had been no vomiting and the bowels had moved since the attack began. Physical examination further revealed the finding of right-sided "intercostal" neuralgia extending over his entire right chest, abdomen and thigh. Despite this finding a bright green gangrenous appendix was removed from a swallow nest position. The patient recovered and the parietal hyperesthesia entirely disappeared.

The appendix may lie in the pelvis and adherent to the urinary bladder under which circumstances painful urination or even retention will confuse the issue. One such case was referred to the writer with the diagnosis of urethral stricture with retention of urine. Appendectomy cured the patient.

Kreutzmann some years ago and recently Randall reports several cases in which an acute appendicitis has been responsible for acute urethral pain referred to the groin, penis and scrotum, accompanied by a few red blood cells in the urine. Royster in his admirable book on appendicitis, reported a case in which the appendiceal abscess had ruptured into the ureter. A difficult diagnosis, preoperatively, we would say. In those cases where the appendix is retroperitoneal lying high up behind the ascending colon, even with the tip just beneath the liver, the diagnosis must be made from pyelitis, or perinephric

abscess or gallbladder disease. In an appendicitis in this region the general abdominal findings are negligible in that there rarely is nausea or vomiting, no general abdominal pain, no anterior tenderness and rigidity and tenderness is limited to the loin. The leukocytes are high, 20,000, the temperature also is high, 102° to 103° F and sometimes a chilly sensation occurs. In the absence of urinary findings this diagnosis should first be retroperitoneal appendicitis.

Occasionally the pain of acute appendicitis begins suddenly over the appendix and persists constantly. This is usually due to a sudden block by a concretion near the base of the viscus. When this is the case perforation usually occurs within a very few hours. Such occurred within six hours in one of the writers' cases.

Rapid and early action is usually necessary in the handling of acute appendicitis that develops during or immediately following a pharyngitis, tonsillitis or other upper respiratory infection. These cases are usually fulminating in character.

Nausea and Vomiting—These symptoms appear in only about 70 per cent of reported cases. They are most often absent in the pelvic, 25 per cent, the retroperitoneal, 34 per cent, and in the extra cecal, 30 per cent type of the disease. When it does occur it comes after the pain and often follows ingestion of medicines. Vomiting is never a prominent symptom and may occur but once or twice—it usually ceases after the pain becomes localized. Should it occur, and with pain, it is an indication of the spread of the disease beyond the appendix either into the peritoneum or into portal system. It is not a dependable sign, being especially unreliable in children and in old people.

Temperature—Again we must consider an unreliable sign. In reported cases it is present in about 70 per cent of cases and in most cases it does not rise above 100.5° F. This is so noticeable that high temperature—103° to 105° F., in adults, should direct attention to extraperitoneal conditions, i. e., pneumonia, pyelitis, influenza, etc. Chills occur in about 5 per cent of appendicitis cases and about 5 per cent of these

develop pylephlebitis Only about 20 per cent of cases have a temperature exceeding 101° F

Leukocytosis—Here again is an untrustworthy single sign Eighteen and six tenths per cent of the counts were below 10,000 and 44 per cent were between 14,000 and 18,000

Bowel History—No dependence can be placed upon bowel action in these cases although the most usual finding will be in the direction of limitation of evacuation Diarrhea does occur both in the beginning of the attack and after it is well under way Gastric enteritis, secondary to improper ingestion or incident to influenza and intestinal infections, can be, and not infrequently are associated with diarrhea Not infrequently the appendix becomes secondarily affected and acute appendicitis then dominates the picture Diarrhea incident to appendiceal abscess and pelvic peritonitis needs no discussion A rectal examination makes the diagnosis

Perforation—This catastrophe occurs early in children, in all cases associated with acute pharyngeal infection and in ulceration near the base of the appendix

Remarks—About 70 per cent of acute appendicitis cases are atypical in one or more of the cardinal symptoms In children and the aged diagnosis is made even more uncertain by reason of the fact that reliable history of pain, tenderness, and rigidity is difficult The atypical case is responsible for a great part of the high mortality that still exists in this most universal disease Burrows in "Mistakes and Accidents in Surgery" says "The majority of misadventures in appendicitis arise in connection with diagnosis The most crafty of experienced practitioners will be deceived now and then The careless and inexperienced will err perpetually"

Finally, our most dependable findings in acute appendicitis are localized pain, tenderness, and rigidity

CLINIC OF DR. MARTIN E. REHFUSS

JEFFERSON HOSPITAL

TREATMENT OF INOPERABLE CANCER

INOPERABLE cancer is always with us. Like the four horse men of the Apocalypse, it rides rough shod throughout the country leaving nothing but devastation in its wake. More than 100,000 people die annually of carcinoma and of this number one third die of carcinoma of the stomach, one of the most insidious forms of this disease. Abdominal cancer, more particularly that of the stomach, pancreas, and colon has been my problem. But cancer anywhere which is inoperable presents similar difficulties. We are committed today to the proposition that cancer is curable when it is diagnosed early and where it is accessible to treatment. Therefore all our efforts are concentrated on early diagnosis. We believe that early diagnosis is possible in many instances by modern methods of study. Two conditions militate against early diagnosis, one, the most important, is the patient who comes late and second, the thorough and complete diagnostic survey which is often done reveals the condition only when symptoms are intractable. Both of these can be improved by educating the public and assisting the practitioner.

What are we to do to the inoperable cases of carcinoma? The case where the ruthless exploration of the surgeon's knife or the tell tale symptoms which the clinician knows as well reveal this state of affairs. What are we to do with these 100,000 or more sufferers every year? Are we to use cross-fire

x-ray or radium in its various forms? That is for you and the roentgenologist to decide. Are we to use colloidal lead, colloidal copper, colloidal gold, or colloidal selenium or anyone of the many suggestions as yet unproven and by no means harmless? Here again you are to be the judge. An honest effort is always salve to one's conscience, but an inoperable cancer patient is a poor subject for experimentation.

I prefer to discuss those questions which to my mind are paramount in the handling of these sufferers. If the art of medicine has anywhere a field of usefulness, it is to smooth the path and the ensuing months of these sufferers in such fashion that they may be free from some of the suffering and the all too gruelling experience that awaits many of them. That we can do this in many ways is attested by the fact that so many of these cases are carried to their graves blissfully ignorant of the cause of their trouble.

The first problem to my mind is to *control the psychology of the case*. Wherever possible the patient should not know his true condition although some responsible member of the family or all the family should be familiar with the whole truth. If ever a white lie was justifiable, it is in the treating of these cases. I remember some years ago having a young man with carcinoma of the stomach explored and found inoperable. Late in the day I was called by the nurse and told that the surgeon had informed the patient that nothing could be done and he promptly collapsed. He almost died. It took us a week to get him under control and then we were able to keep him going for eight months in comparative comfort. I realize that many medical men do not agree with me on this subject but my experience is unalterably opposed to acquainting the patient with his malady. Such a patient is most difficult to handle. If the patient has sufficient confidence to submit to an operation on his physician's advice, he usually has confidence in what the physician will tell him. *The patient must receive an explanation which will satisfy his mind*, otherwise the long days ahead are trying to say the least. I always explain the condition as an inflammation, ulceration or

obstruction such as would naturally satisfy the patient and I see to it that the attendants or family have a similar explanation forthcoming. Furthermore, I usually insert a proviso that the convalescence will be slow and he has to be prepared for that. Regardless of all the talk to the contrary there are few individuals who can take a death sentence like inoperable carcinoma without perceptibly showing the effect. The first job for the physician will be to *get as clear cut a conception of the problem* to the patient as possible, but under no circumstances must this conception be one of malignancy. The average patient will accept perfectly well the statement that a large thickened inflamed ulcerated part of the stomach wall was removed and it will take months to recover, or that there was an obstruction of the bowel with inflammation and adhesions and an extensive operation had to be performed. Such a patient will turn over and fight, but tell him he had an inoperable cancer and notice the difference. Even though he says he wants to be told, no one wants to be given such information. The first and most important part of the care of the inoperable cancer to my mind, is the *mental attitude*.

The second problem particularly in the digestive cases, is the *dietary*. Cancer of the stomach eventually destroys stomach function, progressively reduces the capacity of the organ and is sooner or later attended by pronounced symptoms. Inasmuch as both the mucous membrane with its secretion and the musculature with its peristalsis are impaired, it follows that the business of the stomach, the reduction of food to chyme is seriously interfered with. We can alter this by mechanically reducing food before it is ingested. We can put meat, poultry and fish through a meat grinder, we can put our vegetables through a colander and give them in puree form, the same thing obtains for fruits. We can use the cooked cereals instead of the raw cereals and use various milk modifications. Later on we can use meat extracts instead of meats, progressively reducing the size of our feedings as stomach intolerance increases while we increase the frequency.

Intermittent is often very troublesome. See that there is suf-

ficient vitamin B in the diet Dilute hydrochloric acid, 20 minims, tincture of nux vomica, 10 minims, a compound tincture of gentian, 20 to 30 minims, may be tried or a single mixture like the following through the tube

\mathcal{R} Ac hydrochlor dil	\mathfrak{v}_{iii}
Tinct nucis vomici	\mathfrak{v}_{ii}
Essen pepsin grs	\mathfrak{v}_{iv}

Sig—Dessertspoonful in water through a tube before meals

Such mixtures may prove irritating and then a fine old brandy or whisky, well diluted, may be more helpful An old French formula which I have frequently used is Angostura bitters, 20 to 30 grains, in a little Italian vermouth Anorexia may be due to retention and is occasionally markedly improved by simple gastric lavage twice a day as I shall point out

Some patients go through the entire disease without pain In others pain is an early and severe symptom Pain should always be controlled with mouth medication and where possible with non-narcotic drugs at first One of my favorites is

\mathcal{R} Ext belladonna	gr 1/12
Acetphenetidin	gr \mathfrak{iii}
Bismuth subcarbonat	gr \mathfrak{xii}
Magnesi ox pond	gr \mathfrak{x}
For 1 powder N 24	

Sig—1 powder in water after lunch and dinner

Ac acetyl salicylic acid, 5 grains, and sodium bicarbonate, 5 grains, may be substituted for the acetphenetidin Such a prescription would be

\mathcal{R} Ext belladonna	gr 1/12
Ac acetyl salicylic	gr \mathfrak{v}
Sodium bicarbonat	gr \mathfrak{v}
Bismuth subcarbonat	gr \mathfrak{xii}
Magnesi ox pond	gr \mathfrak{x}
For 1 powder	

If pain increases then the formula can be modified with the addition of codeine sulphate, $\frac{1}{2}$ grain, and the addition of

some local anesthesia like anesthesin or orthoform. Such a formula would be

℞ Ext. belladonna	gr 1/12
Anesthesia	gr 1/2
Acetphenetidin	gr lii
Codeine sulphat.	gr 1/4
Bismuth subcarbonat	gr xli
Magnesia ox. pond.	gr x
For 1 powder	

It is needless to remark that these various preparations can be placed in capsule form. I prefer the powder because it exerts a protective influence as well. I prefer however combinations such as the above that I can vary at will.

When the stomach becomes intolerant and mouth medication is out of the question it is not necessary to resort immediately to hypodermic medication. Many years ago Dr. Gros, in Paris, taught me the use of suppositories for this purpose and the original formula is still a favorite of mine.

℞ Ext. belladonna	gr 1/12
Heroin hydrochloric	gr 1/12
or	
Codeine sulphat	gr 1/2
Acetphenetidin	gr lii
Mefonal	gr v
Or thebutom	gr s
For 1 suppository	

Sodium amytal, 3 to 6 grains, with $\frac{1}{2}$ grain of codeine sulphate and 1 grain of anesthesin is also a valuable suppository formula. While severe pain nearly always calls for morphia hypodermically, there is a capsule when tolerated, which is one of the most remarkable for the relief of severe pain.

℞ Pan of a	gr 1/3
Chauld s	gr 1/3
Codeine sulphat.	gr 1/2
Acetphenetidin	gr v
Codeine sulphat	gr 1/2
For 1 capsule	

This formula is the most powerful I know for arresting pain, even that of pancreatic carcinoma of the type which involves the solar plexus. Of course we can give morphine or codeine tablets alone by mouth and this is common practice. Where possible its use should be restricted to the terminal stages of the malady.

Nausea and vomiting are symptoms particularly with carcinoma of the stomach which may be persistent. I have always been partisan to gastric lavage where used carefully with the fractional tube. I am a believer in the use of lavage morning and night as long as lavage brings up a lot of dirty material and food debris. Our plan is to wash the stomach with a warm solution of bicarbonate of soda, using ordinary siphonage with the barrel of the syringe. Some observers are of the opinion that gastric lavage may promote hemorrhage under the circumstances. I have never seen a severe hemorrhage produced in this way, if caution was used in the technic. It is also of value to use mild disinfection. I prefer the ordinary hexylresorcinol solution (1 1000) diluted three or four times. In our studies, this solution was found to be powerfully bactericidal. Metaphen (1 5000-1 8000) can be used in the same way. Even disinfection with $\frac{1}{4}$ grain of nitrate of silver in distilled water, followed by the instillation of normal saline solution. Nothing equals lavage for nausea and vomiting, particularly where food retention is a prominent factor.

Mild nausea can be treated in one of two ways, by drugs to allay the symptom, or by drugs which tend to cleanse the mucosa or stimulate the liver. An example of the former would be the following capsule

R _x Anesthesia	gr 1/2
Ext hyoscyamus	gr 1/8
Cerū oxalat	gr 1
Phenobarbital	gr 1/2
For 1 capsule	

The French use a mixture of hyoscyamus and strychnia called the anti-nausea pill.

An example of the second class is some modification of the

Bourget formula taken in hot water before meals This is also laxative

℞ Sodii bicarbonat. exsic.

Sodii phosphat. exsic.

Sodii sulphat. exsic.

aa ʒss

Sig.—½ teaspoonful in ½ tumblerful of hot water taken before meals.

When the stomach will tolerate no medication and nausea is severe, the use of the rectal suppositories mentioned under the heading of pain are very effective.

The patient with inoperable carcinoma is nearly always an apprehensive individual Usually mild nerve sedatives and antispasmodics are well borne, take the edge off the nervous irritability and are usually necessary In my hands the bromides and the phenobarbital group are the most satisfactory The best bromide mixture in my experience is a modification of Tessier's as follows

℞ Liq pot arsenatis

gr xxv

Strontii bromide

ʒiiss

Tr hyoscyamii

ʒiiss

Tr gentian co

ʒii

Elix digest. comp

q s. ʒiv

Sig.—Desertspoonful in water before meals.

An example of the phenobarbital prescription

℞ Pulv carbo li-ul

gr ii

Pulv pepsinryme

gr ii

Fel. bavis purifac.

gr 1/2

Ext hyoscyamii

gr 1/12

Phenobarbital

gr 1/2

For 1 capsule

Sig.—1 capsule before meals.

I like one of these formulas can be used for months at a time Occasionally a patient is a little too somnolent with ½ grain phenobarbital dosage and does better with ⅓ to ¼ grain

Weakness and anemia are symptoms sooner or later common to all inoperable forms of carcinoma. Some of my

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confreres believe in *blood transfusions* which at times are of great value. In fact, in some instances, the whole picture changes. I prefer to resort to blood transfusions in these cases only if there has been a severe hemorrhage, or for some reason the blood count has dropped too rapidly and it is obvious that barring accidents, the patient has still some time to live. I know several men who treat all forms of inoperable carcinoma with blood transfusions. *Dehydration* is a bothersome symptom at times, particularly in pyloric obstruction. It may necessitate intravenous injection of salt solution with glucose, or hypodermoclysis. Dehydration and acidosis are symptoms which are more liable to occur after severe attacks of vomiting and for a time may complicate the picture. Tonics may be given at any time or hypodermics. The patient expects and wants something to strengthen him. If a nurse is in attendance the various forms of iron, arsenic and strychnia may be of value, although a pellet of $\frac{1}{60}$ grain of strychnia several times a day may be as beneficial.

Severe diarrhea immediately directs attention to a simplification and modification of the diet. Roughage must be cut out, and a smooth, nonresidue diet substituted. Medically, kaolin, bismuth subcarbonate and the exhibition of small doses 2-3 drops of tincture opii may be sufficient to correct the condition. Occasionally dilute hydrochloric acid is effective.

Inoperable carcinoma of the abdomen frequently presents surgical problems which must be considered. Carcinoma of the pylorus may become obstructive demanding a gastro-enterostomy. Carcinoma of the head of the pancreas may produce an obstructive jaundice which is only relieved by cholecystogastrostomy or cholecystoduodenostomy. Carcinoma of the bowel is a surgical problem from the start, even though it may be inoperable. Colostomy early and later presents a series of problems in which a complete readjustment of the patient's method of living is necessary.

In every case however a judicious rearrangement in the patient's habits is required. Whether bedridden or not, regular hours of diet and rest, with sponging, bathing and a daily

schedule which will be sufficiently comprehensive, are most desirable. The bed patient should seek to conserve strength and should make it a practice when in bed to have regular rest hours after meals, especially two hours after the noonday meal. This means a nap if possible with no visitors, and no diversion, no reading, no radio and the shades pulled down to encourage complete rest. It is just as important for these sufferers as it is for tuberculosis. Plenty of fresh air of course is desirable because it improves the patient's morale and his appetite.

I always like to see the patient who is diverted and can be diverted by hobbies and avocations. Today there are so many ways in which a bedridden patient can amuse himself. For the bedridden patient there are many vistas to occupy the hours of the day, reading of every variety and description, the use of the radio which literally brings the world at your door. Biography, travel, novels offer an endless source of diversion. I remember one man with cancer of the pancreas who could not be diverted until someone gave him six volumes of *Burk* which proved to be of enthralling interest to him. Card games, and particularly the many new ways of playing solitaire are of interest. Several volumes are available at the present time listing fifty or more ways of playing this interesting game. I have always been interested in noting the hobbies of some of these people. I like to have a bowl of gold fish and some growing things in the room. Modern occupational therapy offers many suggestions of interest.

The modern hospital bed, while at first objectionable to the patient soon becomes almost a necessity in some cases. Their width permits tables for radios, books, water, or food to be placed on both sides within easy reach. Their height, as Dr. Watson says enables the patient to talk to others without the constant strain of looking up. Furthermore, their double action permits the patient to be placed in almost any position without the ensuing strain so often found in the ordinary bed.

As in all cases of this type, it is necessary that the patient inform the physician of any untoward occurrence. Sudden pain, a stiff joint, hemorrhage, sudden weakness, an u

plained attack of vomiting, bowel impaction, an unexplained temperature or pulse rise will be the signal for the physician. Nearly always the nurse or the family must be coached in the handling of the case.

I have never seen a primary carcinoma of the stomach, pancreas or bowel, which was cured by x -ray treatment. On the other hand I have seen remarkable changes in pulmonary, gland and bone metastases. In the latter condition a pathological fracture can sometimes be averted and marked improvement noted in the condition. I make it a rule to control local metastases in this way. Dr. Manges has been most successful in some of this work, although it must be realized that such methods are merely palliative. When they succeed in relieving discomfort or severe pain or in averting more serious accidents, they can contribute in this way to a far better handling of the case. On the other hand I have given up the treatment of primary carcinoma of the stomach, pancreas and bowel by deep x -ray therapy.

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CLINIC OF DRS CHARLES MAZER AND S LEON
ISRAEL

FROM THE DEPARTMENT OF GYNECOLOGY, MOUNT SINAI
HOSPITAL

THE SYMPTOMS AND TREATMENT OF THE MENOPAUSE

and the corpus luteum, the latter is the first to suffer from the progressive sclerosis of the menopausal age. Thickening of the ovarian tunic offers a hindrance to rupture of the graafian follicles as they mature, resulting in follicle cysts and in the elimination of the corpus luteum as a factor in the control of the menstrual cycle. The abnormal uterine bleeding that often follows in the absence of the corpus luteum hormone, progesterin, is not the only symptom of the oncoming climacteric. Evidence of neurocirculatory instability may accompany and even precede the abnormal uterine bleeding, indicating that the corpus luteum hormone which is the first to disappear in the climacteric is an important factor in the maintenance of normal endocrine interrelationship and that its absence partly accounts for the constitutional as well as the uterine symptoms of the menopause. The presence of normal or near normal quantities of the follicular hormone, estrin, in the urine of some women suffering from severe climacteric symptoms (Kurzrok² and Frank³) is supportive of this view.

The Pituitary Factor—The changes in the interrelated glands following castration of the human are most constant and prominent in the anterior pituitary lobe (Tandler and Gross,⁴ and Rossle⁵). They consist of an increase in the acidophiles and in the appearance of a modified form of basophiles (castration cells). The structural response of the anterior pituitary lobe to castration is greater than to the gradual decline of gonadal function of the natural menopause, probably because of the *sudden* withdrawal of ovarian inhibition. The pituitary changes do not appear immediately after castration even in the animal. In the rat, for instance, there is a lapse of three weeks between castration and the appearance of castration cells (Dohrn and Hohlweg⁶).

Pituitary-ovarian Interrelationship—The intimate pituitary-ovarian interrelationship was definitely established experimentally and clinically during the past decade. It was found that the anterior pituitary lobe produces, in addition to the growth, thyroid, adrenal, lactation and parathyroid stimulating hormones, a principle (or principles) which initiates

and maintains gonadal function by direct stimulation of the ovarian follicles to mature, ovulate and luteinize. It was further established that the maturing ovarian follicle produces estrin and that its successor, the corpus luteum, produces, in addition to estrin, another hormone, progesterin. The two jointly rebuild the endometrium after the dismantling process of menstruation. Effective pituitary stimulation of the ovary is, however, predicated by the state of responsiveness of the ovary. Thus, for instance, no amount of anterior pituitary sex hormone can evoke a response in the ovaries of rats less than eighteen days old (Colbip⁷). The ovaries of menopausal women are likewise incapable of responding to the excess quantities of the pituitary sex hormone usually present in the blood and urine at this age (Fluhmann⁸ and Mazer⁹).

The ovarian hormone, estrin (probably also progesterin), at a certain level of concentration inhibits pituitary function. Thus, the removal of its influence by means of castration is followed by an increase in the structural and functional activities of the anterior pituitary lobe (Engle¹⁰ and Evans¹¹) which can be prevented or corrected by the administration of the ovarian hormone, estrin (Meyer *et al*¹² and Hohlweg¹³). The parallelism between the pituitary hyperfunction of castration and that of the menopause, occurring in response to lack of estrin inhibition, is evident by the presence of an excess of the gonad-stimulating hormone in the blood and urine of both castrates and those who have reached the natural menopause.

Ovarian deficiency and castration at an early age are not accompanied by the pituitary reaction seen in climacteric women and in those castrated after the pituitary-ovarian interrelationship was well established. The youngest woman presenting the typical syndrome of the menopause after castration in our experience, was no more than twenty-two years old. It seems that the dependence of the pituitary gland upon ovarian control is acquired during adolescence. Before the establishment of this dependency, the pituitary gland can apparently function normally without the controlling influence of the ovarian hormones.

The pituitary hyperactivity resulting from removal of ovarian inhibition is apparently not restricted to the sex stimulating cells. For instance, the function of lactation, which is under the control of the anterior pituitary lobe, is prolonged and quantitatively increased by castration of the cow and is inhibited in the rat by the administration of the ovarian hormone, estrin (Parkes¹⁴). In the human, untimely lactation can likewise be suppressed by the administration of large doses of estrin (Mazer and Israel¹⁵). Similarly, can the diabetic glycosuria of depancreatectomized dogs be reduced considerably by the administration of the hormone, estrin (Barnes¹⁶), indicating that the two respective functions (lactation-stimulating and diabetogenic) of the anterior pituitary lobe are inhibited by the presence of the ovarian hormone and increased by its absence. This probably explains some instances of hyperglycemia, so frequent in these years, as well as the abnormal breast hyperplasia and benign nipple bleeding occasionally seen with the advent of the menopause (Mazer¹⁷).

The Thyroid and Adrenals—A hyperfunction of the anterior pituitary lobe resulting from removal of ovarian inhibition can and, in some instances, does cause increased activity of the thyroid and adrenals, inasmuch as these glands depend largely upon the stimuli derived, respectively, from the thyreotropic and adrenotropic hormones of the anterior pituitary lobe (Collip¹⁸). Variations in response of the participating glands depend upon their previous functional states and upon intermediary modifying factors. If these are properly discounted, the sequence of events, as described above, conforms to the clinical picture of the climacteric.

In the woman castrated *during adult life*, it is common to see more or less apparent thyroid hypertrophy (Maranon¹⁹). This thyroid hypertrophy is probably caused by an excess production of the thyreotropic hormone of the hyperactive anterior pituitary lobe and is in contradistinction to the tendency to atrophy of the thyroid so often seen in the young castrate (Tandler and Gross²⁰). The size of the thyroid is, however, really independent of its functional capacity. We

must therefore determine the functional state of the thyroid during the climacteric by proper interpretation of symptoms. The emotional states, the facial expression of fright, a pulse rate of 90 or more and the loss of weight seen in some of these patients are apparently due to a hyperthyroidism. Whether the hyperthyroid response of the menopause will be explosive or almost indiscernible also depends upon the predisposition of the woman. The thyroids of the nervous, vehement and active women and those with simple goiters react adversely. On reaching the critical age, these women often become frankly hyperthyroid.

The paroxysmal tachycardia, palpitation of the heart and other vasomotor symptoms of the climacteric are, however, apparently the result of the direct stimulative effect of the anterior pituitary lobe hormones upon the sympathetic division of the autonomic nervous system which, in turn, excites the production of an increased amount of adrenalin. This is suggested by the experimental work of Marine²¹ who produced excitation of the sympathetic division of the autonomic nervous system in thyroidectomized animals by the administration of anterior pituitary lobe extract.

Intermittent and increased production of adrenalin, acting upon a sensitized sympathetic division of the vegetative nervous system, seems to explain most of the extragenital phenomena of the climacteric which are, to a degree, similar to the clinical manifestations of the hyperadrenalemia seen in patients with chromaffin cell tumors of the adrenal medulla. When the latter condition is well developed, paroxysmal hypertension, tachycardia, vasoconstriction followed by vasodilation (pallor and flushing of the skin), headache, choking sensation and glycosuria are the outstanding symptoms. These facts, coupled with the unusual sensitiveness of menopausal women to injections of adrenalin (Hannan,²² and Myers and King²³), indicate that the vasomotor instability and the blood pressure variations of the climacteric are due to a hyperadrenalemia. Whether the adrenal medulla is stimulated to increased function by the hyperfunctioning pituitary lobe directly or through

the medium of the sympathetic division of the autonomic nervous system is still unknown

Hyperfunction of the suprarenal cortex at the climacteric is clinically evident in certain women by the development of secondary male sex characteristics, such as changes in physical form of the body, alterations in the voice and the appearance of facial hair. It may also partly account for the obesity often present in the climacteric.

The Rôle of the Vegetative Nervous System in the Climacteric—The endocrine reorganization due to ovarian deficiency plus the pluriglandular reaction which it establishes are undoubtedly the directing forces in the production of the menopausal syndrome. The instability of the vegetative nervous system so prominent in this condition is secondary and sequential, and not primary and causative. The vegetative nervous system consisting of two antagonistic divisions (sympathetic and parasympathetic) is largely under the control of the hormones produced by the several interrelated glands concerned in the syndrome of the menopause. Adrenalin, the hormone of the adrenal medulla, stimulates, reinforces and may even supplant the sympathetic division of the vegetative nervous system (Cannon²⁴).

With few exceptions, the blood vessels and the sweat glands, so active in the climacteric, are controlled by the sympathetic division of the vegetative nervous system. Whether contraction and relaxation of the blood vessels depend upon the degree of the stimulus or whether there are genuine dilator fibers in the sympathetic division is not known. Hoskins²⁷ has shown experimentally that adrenalin, through sympathetic control, exerts a biphasic effect on blood pressure—subminimal stimulation causes inhibition of the sympathetics and relaxation of the blood vessels.

In summarizing the neuroendocrine mechanism concerned in the production of the menopausal syndrome, we may postulate that the pituitary hyperfunction resulting from the removal of ovarian inhibition evokes the following reactions

- 1 Excitation of the sympathetic center in the midbrain

2 Stimulation of adrenalin production, either through the medium of the sympathetic division of the vegetative nervous system or through direct influence upon the medullary structure of the adrenals

3 Stimulation of the adrenal cortex, evident in some by the development of secondary male sex characteristics to a mild degree

4 Stimulation of the thyroid in patients predisposed to hyperthyroidism

The Time of the Climacteric—The time of onset of the menopausal syndrome has been variously estimated by competent observers. The individual conception of what symptoms constitute the beginning of the climacteric accounts for the differences of opinion. If, for instance, neurocirculatory disturbances without an organic basis be taken as criteria of the onset of the climacteric, the estimate of 40.8 years given by Werner⁶ is, in our experience, more nearly correct than those of Sanes,⁷ Norris⁸ and others whose average estimate of forty-six years is based upon the time of appearance of menstrual irregularities or total cessation of menstruation. The neurocirculatory symptoms often appear long before the latter and even while the woman is still menstruating regularly. The neurocirculatory and associated mental symptoms often appear when there is still an ample production of estrin but a total absence of the corpus luteum and its hormone, progesterin (ovarian dysfunction or imbalance). The estrin elaborated by the cyst forming, graafian follicles evokes almost rhythmical uterine bleeding. Episodes of prolonged and excessive bleeding, likewise occur because of the absence of the corpus luteum hormone progesterin.

The time of onset of the climacteric and its severity are also materially influenced by racial and climatic factors and by the previous endocrine potency of the ovary. Women who during their active sexual life showed evidence of ovarian insufficiency such as a late onset of the menarche, irregularity of menstruation, frigidity, dysmenorrhea and sterility without apparent cause, approach the menopause at an earlier age and

go through it with fewer disturbances than those who were sexually active

Symptomatology—In a description of the symptoms of the climacteric, a distinction must be drawn between the manifestations of the menopause *per se* and those due to antecedent instability of the nervous system coupled with the various organ changes occasioned by the declining years of the middle age. In the latter category are grouped the early manifestations of hypertensive and arteriosclerotic cardiovascular disease, genital carcinoma, diabetes mellitus and presbyopia. The simultaneous existence of these diseases of age complicates the diagnosis of the purely menopausal syndrome.

The severity of the symptoms of the natural menopause varies with each individual. It has been roughly estimated that two thirds of women escape the severe mental and physical strain which their more unfortunate sisters experience during the menopausal years. The syndrome more commonly follows surgical or irradiation castration. Peterson²⁰ estimates that only 10 per cent of women escape the rigors of the artificial menopause. The variations in the severity of the symptoms are unquestionably influenced by the individual constitution, temperament, the emotional make-up of the individual and the presence or absence of pre-existing or concomitant diseases.

The symptoms of the menopause are best discussed when genetically grouped. However, it must be remembered that overlapping does occur and that borderline inaccuracies of description must appear inasmuch as the symptomatology is essentially subjective in character. They may be subdivided as follows: Genital (amenorrhea, metrorrhagia, disturbances of libido, and changes of the secondary sex characteristics), circulatory (flushes, chills, cold sweats, palpitation and blood pressure variations), and neuropsychiatric (insomnia, vertigo, tinnitus, auras preceding the flushes, emotional states, paresthesias, headache, melancholia and suicidal mania).

Genital Symptoms of the Menopause—As stated previously, genital symptoms, such as irregularity of menstrua-

tion, metrorrhagia and amenorrhea, usually appear late in the climacteric. They are, however, the most characteristic and often the only evidence of ovarian decline. Termination of the menstrual function may occasionally be abrupt, usually the bleeding becomes irregular and scanty while the intervals gradually lengthen until complete amenorrhea ensues. The transition, according to Norris,²⁸ covers a period of twelve months in 68 per cent of women and sixteen months in 5 per cent.

course The urethral meatus participates in the involutional process and is often the seat of stricture

Complete cessation of ovarian function produces regression of the secondary sex characteristics and, in some, suggestive signs of virilism The breast tissue atrophies and, in the obese, is replaced by relaxed fat tissue The axillary and pubic hairs become scanty but a crop of facial hair often appears

Libido is usually not materially influenced by the climacteric Only a few of the many climacteric women who have come under our observation in the course of two decades complained of a change in libido A very disturbing, though rare phenomenon, is the sudden development of intense and irresistible desire for coitus (nymphomania) in women who were heretofore normal and whose mates of their own age or older are no longer capable of meeting the newly acquired needs of their wives We have encountered this condition only twice in menopausal women One whose blood and urine were studied carefully for the follicular hormone content showed repeatedly a mouse unit in an extract of 30 cc of blood and 21 rat units in the twenty-four-hour output of urine—certainly an excess production of the hormone in a woman who had not menstruated for two years The absence of menstruation, despite the excess production of the follicular hormone, was apparently due to the inability of the endometrium to concentrate the hormone

While this observation and those of Werner and Collier³⁰ seem to point to a definite relationship between the amount of estrin in the circulating blood and the state of libido, we have not encountered a single case of artificially induced nymphomania in our vast experience with the administration of huge doses of estrin over long periods Only a few of the many thus treated experienced a slight increase of libido

Menopausal Uterine Bleeding—During the period of transition from menstrual regularity to permanent amenorrhea, there often occur episodes of metrorrhagia, occasionally of an alarming character Even when the loss of blood is not sub-

stantial, the abnormal uterine bleeding is most disturbing because of the possible presence of malignancy. The latter in our experience is more often encountered in menopausal women who still menstruate regularly than in those who show a tendency to delay in the flow. Malignancy can be ruled out only by an exploratory intra uterine curettage and biopsy of cervical tissue.

The benign uterine bleeding of the menopause is due to a break in the normal ovarian cycle, namely, the prolonged, though not necessarily excessive, production of estrin by the follicle cysts, invariably present in this condition, and the absence of the balancing and controlling influence of the corpus luteum and its hormone, progesterin. The resultant endometrial hyperplasia and necrosis are the immediate causes of the abnormal uterine bleeding of the menopause.

Organotherapy in the functional uterine bleeding of menopausal women is usually ineffective because the decline of ovarian function is due to cellular changes within the ovaries incident to age. Senile ovaries are not responsive to stimulation by the anterior pituitary like substance (antuitrin S, follicle-in, A P L) usually employed in the treatment of functional uterine bleeding of younger women.

Abnormal uterine bleeding at or near the menopause, when malignancy is often encountered, should be treated by means of an exploratory uterine curettage and the application of 600 to 1200 mg. hours of radium. This procedure is both diagnostic and curative. If the endometrium shows evidence of malignancy, subsequent hysterectomy is the logical measure to employ.

Circulatory Symptoms—The most characteristic symptom of the menopausal period is the so-called "flush" also described as a heat flash or a suffocating feeling. It is, perhaps the one pathognomonic symptom of the menopause since it occurs in no other ailment. The flush may appear as often as every ten minutes and is one of the causes of severe insomnia in the climacteric. Rarely, the flush occurs without warning and free of other phenomena. Usually, there is a

characteristic sensation of epigastric warmth or an aura of slight nausea, which is immediately followed by a wave of heat and visible, though momentary, erythema of the face, neck and anterior part of upper chest. Usually, the flush is immediately followed by a cold sweat and momentary chill. These recurring spells of heat and cold keep the patient awake in an attempt to regulate the amount of bed covers. Occasionally, the cold sweat and chill appear in the absence of a flush. It is this triad, flushes, cold sweats and insomnia, more than any other single symptom that brings the menopausal woman to the physician begging for relief.

A vasomotor phenomenon, observed by these patients less frequently than the flushes, is palpitation. It seems to bear no relation to the incidence and frequency of the flushes and occurs without any evident cardiac lesion. Tachycardia is often observed by the physician to be the basis of the palpitation. The objective paroxysmal tachycardia and the distressing subjective palpitation are often accompanied by a moderate dyspnea. This symptom complex appears more frequently as a result of unusual exertion. Werner²⁶ has aptly compared it to the so-called "effort syndrome" of neurocirculatory asthenia.

The blood pressure variations which may occur at the time of the menopause are the subject of much dispute. There is an undoubted incidence of hypertension at the time of the menopause, but the climacteric age is also the age when arteriolar and nephritic changes become manifest. There is, however, a definite instability of the blood pressure which may vary hourly from low to high levels, independent of organic vascular changes. Instability is typical of the entire menopausal syndrome and is due to the reactions of the vegetative and central nervous systems to the pluriglandular rearrangement incident to the menopause.

Neuropsychiatric Symptoms—Similarly, characteristic of the menopause are the neuropsychiatric disturbances often encountered. The neurologic manifestations and psychic disorders, prone to enter into protean symptomatology of the

menopause, are legion. They are as common in one form or another as the flush. The entire realm of nervous and psychic reactions are easily disturbed by minimal stimuli (Maranon¹⁸). In an analysis of the symptomatology presented by 32 climacteric women, Sevringhaus²¹ found that 16 had various paresthesias, 19 suffered from severe insomnia, and that 17 had abnormal psychic reactions. This closely parallels our experience with a similar number of cases recently studied from the standpoint of hormone therapy. We found 15 patients complaining of various paresthesias, 20 of insomnia, and 16 of psychic manifestations, such as melancholia and suicidal tendencies.

Headache is a frequent complaint in those who have other pronounced symptoms of the climacteric. Ten of our 33 patients complained of severe headaches with the advent of the menopause, described by some of them as "the blows of a hammer." The so-called "menopausal headache" (occipitocervical) is, in our experience, rare. Werner,²² however, found that 50 per cent of castrated women and 38 per cent of the naturally climacteric women point to the occipitocervical region as the site of pain.

paresthesias are part of a refractory type of neuralgia (Pisk³²), affecting the small joints and knees with persistent tingling. The so-called "menopausal arthritis" (arthropathia ovaripriva) has been ascribed both to vascular spasm and to a nervous response incident to changes of temperature (Lauber and Ramm³³).

Of the neurologic manifestations, tinnitus and vertigo are not the least annoying. The latter is the more common, and was a major complaint in 5 of our 33 patients. It may be constant or evanescent, diurnal or nocturnal, when at rest or in motion. A very interesting variety of vertigo occasionally described by the patient is a sensation of "swimming in the air" or partial intoxication (pseudonarcotism). In his excellent study of climacteric vertigo, Sanes²⁷ ascribes the sensation to a moderate hypertension. In 66 per cent of 102 patients exhibiting this symptom, he found systolic pressures of 150 to 160 mm. In the small series of cases herein reported and in a larger group not included in the present study, we did not observe any constant relation between the vertigo and the labile hypertension.

Insomnia is a very distressing factor in the symptomatology and is present in more than two-thirds of women suffering from climacteric manifestations. The patients are usually able to fall asleep but are awakened during the early hours of the morning and thereafter are unable to sleep (Sevringhaus³¹). The flushes of heat and the cold sweats are not the only factors in disturbing their sleep.

Disturbances of the psyche are, perhaps, the most interesting of all the climacteric changes. They are characterized by a state of erethism—depression, agitation and apprehension (Jameison and Wall³⁴). Psychic manifestations occur in practically all menopausal patients but, in most, they do not reach a pathologic degree. The background of the patient plays a major rôle in determining how much the psyche will react to the climacteric. In fact, Culbertson³⁵ believes that the psychic symptoms are merely manifestations of a previously existing abnormal mental state. In a study of the neurological

symptoms of 112 surgically castrated women, Gordon²⁰ found that severe psychic disorders developed in the 34 who before operation had manifested some neurologic symptoms

Among the milder manifestations of a changed mental status during the climacteric may be mentioned mental depression, crying spells, apprehension, extreme irritability and impatience, a newly acquired coldness of demeanor and inattention to dress

The psychic changes may proceed to a definitely pathological degree in that the patient no longer has mere varieties of moods, but actually develops delusions. When present, the delusions are those of impending calamity or death. Any of the functional psychoses may occur at this period, but the most frequently observed is that of involutional melancholia. The patient is constantly depressed and is haunted by terrifying visions of disaster. Occasionally, a state of confusion accompanies and heightens the syndrome. Suicidal attempts by women who have reached this state of pathological melancholia has come to be a recognized manifestation of the climacteric. In our small series, 6 patients exhibited severe melancholia and, of these, 3 attempted suicide. Until recent years these severe psychic reactions of the climacteric received little attention. With the advent of our newer knowledge of endocrine interaction and with the recent developments in the field of organotherapy, the literature on neurology and psychiatry is replete with reports presenting this phase of the climacteric and of the excellent results obtained by means of estrogen therapy (Jamelson and Wall²¹ Werner *et al*,²² Bowman and Bender²³ and others).

Prophylactic Treatment of the Climacteric.—The symptoms of the climacteric are not static. They appear and disappear after several years, often leaving the patient in a state of chronic exhaustion. Only one third of women entering the natural menopause require medical attention. These and the majority of women castrated before the forty-fifth year often develop symptoms of an intensity that lead to psychosis if not properly managed.

As a prophylactic measure after castration of the middle-aged, the daily oral administration for a long time of a quantity of estrin sufficient to maintain a near normal blood-estrin level will prevent the consequences of a sudden endocrine imbalance. The daily quantity required to attain this objective varies with the mode of administration and the product employed. When used as a prophylactic, the oral administration of the hormone has many practical advantages over the hypodermic route. Since the objective of treatment is first to maintain a normal blood-estrin level and then gradually decrease this level until the economy has become accustomed to function on minimal doses or on none at all, the hypodermic use of estrin is not feasible as a prophylactic measure. If, for instance, an injection of 1000 rat units of estrin is given every third day, there will be a superabundance of the hormone in the circulating blood during the first day and a marked deficiency thereof during the third day, rendering it impossible to taper off the dose gradually. If, on the other hand, the patient is given 600 rat units of the dihydrofollicular hormone daily, in three divided doses, the blood-estrin level, as determined by the Frank and Goldberger test, and the amount excreted daily through the urine is that normally current during the premenstruum. It is then an easy matter to decrease the dose very gradually and thereby maintain a steady but gradually lowered blood-estrin level. A somewhat larger dose of theelol is required to produce the same effect. These values were determined by us through blood and urine studies of castrated women who had received varying doses of these products.

Treatment of the Climacteric Syndrome—The woman in whom marked manifestations of the climacteric has already developed must be treated on a different basis, for in her we must undo or counteract the established endocrine reactions responsible for the symptoms. In the rat, for instance, it requires much more estrin to correct the pituitary castration changes than to prevent their occurrence (Hohlweg¹³). Therefore, it logically follows that the woman with well-established

disease and about the type of life he should lead afterward, if he is to remain well

3 The segregation of open cases of tuberculosis which are a menace to the community

In the present-day treatment of pulmonary tuberculosis with the increasing importance of collapse therapy and the diminishing importance of climate, the general hospital combined with home treatment can play a more important rôle in the general scheme of tuberculosis control. With this combination the treatment offered compares favorably with the best that any sanatorium can offer.

The following is the general outline for the handling of tuberculosis patients at home. This is of necessity flexible, due to the variability of patients as they are seen. The initial study should include complete physical examination, sputum examination and chest roentgenogram. Sedimentation rate, blood count and urinalysis will give added information. On the findings of these examinations the important indications can be determined. If the disease is minimal or moderately advanced without cavity, bed rest alone is indicated.

SPECIFIC TREATMENT

Rest—When ordering a patient to bed one should give detail instructions. The intensity of the rest depends on the severity of the symptoms and the extent and type of the disease. We divide them into

1 Strict bed rest—which means absolute rest in bed, in which the patient is not allowed to do anything for himself

2 Ordinary bed rest—which means twenty-four hours in bed. The patient is allowed to feed himself and take care of his own toilet, with varying amounts of reading, writing, etc

3 Ordinary bed rest with bathroom privileges

Every patient with definite symptoms of activity should begin with strict bed rest and every patient should be kept in bed from one to three months. During the period of bed rest the patient should be taught to keep his own records and for that purpose a "record book for tuberculosis patients," published by the Journal of Outdoor Life, is usually recommended. This is also the time to educate the patient in regard to his disease, for which there is a wealth of approved literature available. Before a patient is allowed out of bed his initial studies should be repeated. If symptoms of activity continue the studies should be repeated at intervals of one to three months, the future care of the patient depending on the findings of these examinations. After an initial period of bed rest the patient may gradually be returned to reasonable activity within three to six months, providing his check-up examinations are satisfactory.

Diet—There have been a number of special diets advised for tuberculosis. However, there is little proof that they are of any special benefit. The patient should have three well-balanced meals daily, including all varieties of food and at least 1 quart of milk daily. Cod liver oil in some form is a worthwhile addition.

Drugs—There are no drugs of specific value in treating tuberculosis at this time. However they may be used for symptomatic relief. Mild sedatives are helpful to the patient

adjusting himself to the initial period of bed rest but habit-forming drugs should be avoided

This regime is applicable only in early cases of pulmonary tuberculosis. Unfortunately most patients show advanced disease with cavity formation when they are first recognized. Here we are faced with a more difficult problem. An initial period of bed rest should be tried, but too frequently it is not sufficient to cause an arrest of the disease and other forms of treatment must be resorted to. In this type of patient hospitalization in the most conveniently located general hospital is advisable, and some form of collapse therapy considered and carried out if indicated. The length of time the patient should stay in the hospital depends upon the type of collapse used. If a phrenicectomy is done, usually a day or two in the hospital is sufficient. Pneumothorax may be instituted and after a reasonable period of hospitalization the patient can continue treatment at home, in a clinic or in the physician's office. Bilateral pneumothorax should be instituted only under hospital supervision. The period of bed rest following thorocoplasty can well be taken at home under the schedule of strict bed rest.

SUMMARY AND CONCLUSIONS

As a general rule sanatorium treatment is to be preferred because of the danger of contact infection and the fact that the patient can be treated more economically and perhaps more efficiently when grouped together. However home treatment of pulmonary tuberculosis has a definite place in the general scheme of tuberculosis control for the following reasons: (1) There are insufficient sanatorium beds to care for the present number of active cases of pulmonary tuberculosis. (2) Many patients are temperamentally unsuited to sanatorium treatment. (3) The patient in many instances can be better controlled at home. (4) When a patient cures at home the entire family are made tuberculosis conscious and the regulation of his life thereafter is more easily made.

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CONVULSIONS SOME CONSIDERATIONS FROM THE VIEWPOINT OF THE INTERNIST

THE internist deals less frequently with convulsive states than do workers in some other fields of medicine. Fits are daily fare to the pediatrician. The neurologist sees most of the adult patients who suffer from fits, largely his is the diagnosis and almost as largely the treatment, of such conditions as major and minor epilepsy, tumor and abscess of the brain, the results of injury to the brain, advanced intracranial arteriosclerosis, and hysteria. There are, however, a number of convulsive syndromes which properly come within the field of internal medicine. It is the purpose of the present discussion to review briefly, in a clinical fashion, some of the more important, or the more noteworthy, of these.

Hypoglycemia, as a cause of convulsive seizures, is at the present time particularly deserving of attention. Hypoglycemic reactions, other than those induced by overdosage of insulin in the treatment of diabetes mellitus, were first described by Seale Harris in 1924.¹ His conception of the cause of the syndrome was functional over activity of the islet cells of the pancreas, with production of excessive amounts of insulin—the physiologic opposite of pancreatic diabetes. Hence he coined the names "hyperinsulinism" and "hypoinsulinism." Tumor—adenoma or carcinoma—of islet tissue in cases of hyperinsulinism were soon recognized,^{2, 3, 4} and surgical removal was successful in giving relief of symptoms.² Overproduction of insulin is by no means the only cause of "spontaneous" hypoglycemia. Harris⁴ lists also the following causes

- 1 Deficient formation of glycogen in the liver, in certain forms of hepatitis and in massive tumor of the liver

- 2 Hypofunction of the adrenals, interfering with labilization of glycogen

- 3 Ovarian dysfunction

- 4 Pituitary dysfunction

Hypoglycemic reactions have long been known to occur in diabetes mellitus, independently of the administration of insulin, and Zeckwer⁷ has pointed out one way in which they may occur. In her case, pancreatic calculi had caused practically complete loss of the external secretion of the pancreas; the consequent impairment of digestion in the intestine had led to such a degree of degeneration (partially fatty) of the liver that glycogenesis must have been grossly deficient; she believes that undernutrition is an important additional factor. Long-continued and violent physical exertion may cause hypoglycemia, for instance, in Marathon runners or in mountain climbers.⁸

When hypoglycemia is severe enough to cause convulsions, the seizure is usually generalized and clonic, resembling that in idiopathic epilepsy. There are, however, many variants of the fit, and as has been repeatedly pointed out, all kinds of neurologic manifestations, other than convulsions, occur.⁹ Weakness, mental confusion, delirium, coma, personality changes, transient hemiplegia. With the passage of time, there have been many reports concerning hypoglycemic reactions, so that the number of cases in the literature must have mounted into the hundreds. Nevertheless, it is probable that the diagnosis is often missed. The writer wishes particularly to stress the importance of bearing in mind the possibility of hypoglycemia, in studying obscure cases marked by convulsions or other neurologic and psychiatric symptoms. The diagnosis of idiopathic epilepsy should never be made, especially if the onset of fits is in adult life, until the possibility of hypoglycemia has been eliminated. Fortunately, the diagnosis is an easy one to make, a blood specimen taken at the time of the seizure will show great reduction of the sugar content (almost always

below 60 mg per 100 cc, sometimes 20 or 30 mg per 100 cc.), and in the hyperinsulinism type, a glucose tolerance test will show a flat curve falling well below normal values toward the end of the test. In hypoglycemia due to other causes than hyperinsulinism, diagnosis of the underlying defect may be difficult, but other features of the case will point to it, the hypoglycemia itself should be readily recognizable.

The treatment of the acute hypoglycemic reaction obviously lies in supplying carbohydrate to the patient. If he can be persuaded to swallow, he should be given sweetened orange juice, or coffee, or candy, or indeed any kind of food if these are not available, commercial compressed tablets of glucose* are convenient and may be carried by the patient in case of need. If the patient is unable to swallow, the intravenous injection of 20 to 50 Gm of glucose is indicated, the commercially prepared ampules containing 50 cc. of 50 per cent glucose solution are convenient. In urgent cases, when facilities for intravenous injection of glucose are not at hand, subcutaneous injection of epinephrine may give relief by mobilizing liver glycogen and thus raising the blood sugar.

When hyperinsulinism was first recognized, attempts were made to control it by giving a carbohydrate rich diet, with frequent feedings. This regime defeats its own purpose, the high carbohydrate intake further stimulates the production of insulin and the hypoglycemia recurs more frequently and more severely. The carbohydrate should be considerably restricted, and fed mainly in the form of 5 per cent and 10 per cent vegetables, the customary amount of protein may be allowed, and fat will usually have to be high in order to make up the caloric requirement. Patients do better on this regime, and often show progressive decrease in the severity of the hyperinsulinism. John¹⁴ has suggested the administration of small doses of insulin (tentatively, 10 units) after meals, with the idea that if insulin is thus supplied the pancreas will not be stimulated to produce excessive amounts of endogenous insulin.

* Laksy's Dextro-lak made by South Alife and French Laboratories, 1 cent 1 Gm. each of 50 mg. in the experiment capsules.

in his one published case favorable results were obtained. If, in a case of hyperinsulinism, satisfactory improvement is not obtained by these methods, tumor of the pancreas should be suspected and laparotomy should be resorted to promptly. Whipple¹¹ has recently described improvements in the technic of pancreatic surgery which favorably influence results.

Hypoglycemic reactions occurring in diabetes mellitus and due to disproportion between insulin dosage and food intake do not differ in any essential respect from the "spontaneous" variety.

Uremia (literally, "urine in the blood") may be defined briefly as the condition resulting from renal insufficiency with retention of excretory products. For many years the term was applied to almost any of the late manifestations of severe renal disease, but especially to convulsive seizures. Volhard¹² restricted his use of the term uremia (or "true uremia") to the symptom-complex resulting from severe failure of the excretory function of the kidneys, with consequent retention of toxic waste substances, realizing that convulsive seizures may occur in the course of acute or chronic disease of the kidneys in the absence of greatly increased amounts of nonprotein nitrogen in the blood, he applied to these manifestations the name "pseudo-uremia." For this syndrome, Elwyn¹³ uses the expression "acute convulsive" or "eclamptic" uremia. Since Volhard's separation of these two types of so-called uremia, most other students of the subject have concurred in his view.

True uremia occurs most typically in the end-stages of chronic glomerulo-nephritis, but any of the many causes which seriously or persistently hamper the kidney in its work of excretion may eventuate in uremia. Sclerosis of the smaller arterial vessels of the kidney (renal arteriolosclerosis, or arteriolar nephrosclerosis) leads, in a relatively small proportion of instances, to renal insufficiency and uremia, another vascular disease marked by a nephritic picture and sometimes by uremia is periarteritis nodosa.¹⁴ The acute destructive nephroses, such as that induced by mercury, terminate in

menopausal symptoms requires many times more of the hormone for the relief of the symptoms than the amount normally present in the blood. This explains the failure to control severe menopausal symptoms with small doses or large doses given for a short period (Pratt³⁰). An inkling as to the time required to overcome the pituitary hyperfunction and the resultant symptoms of the well established menopause, even with the use of large doses of estrin, may be obtained by quantitative determination of the anterior pituitary sex hormone content of the urine before and during treatment. *It usually takes a month of intensive treatment to reduce the pituitary hormone content of the urine to a normal level. This corresponds in time with clinical evidence of improvement.*

Most of the reported failures to control severe menopausal symptoms with the use of estrin, we believe, are due to inadequate dosage, too short periods of treatment and errors in diagnosis. Dosage should depend entirely upon the severity of the symptoms and the duration of treatment. Even relatively small doses administered for a long time will eventually control the symptoms (Werner and Collier³⁰ and Sevringhaus⁴⁰). However, we have repeatedly seen recurrences of easily controllable symptoms because treatment was discontinued too soon. The best results are, in our experience, obtained with preliminary huge doses, such as 10,000 rat units (50,000 international units) given hypodermically every fourth day. With these quantities the majority of the most annoying symptoms are usually relieved within a period of three weeks, *if the symptoms are truly menopausal* and not due to antecedent or present pathological states unrelated to the climacteric.

In reference to diagnosis, we must remember that many symptoms of the climacteric age such as vertigo, impairment of memory, insomnia and palpitation may be the result of concomitant cardiorenal vascular changes. In the presence of these conditions estrin therapy is bound to fail and receive undeserved discredit. The smaller incidence of degenerative cardiorenal lesions in castrates accounts for the better results with estrin therapy in these patients (Fisher⁴¹).

The question of possible constitutional harm resulting from the administration of such huge doses of the hormone was carefully studied by us ⁴² It was found that the weight, blood pressure, cell count, coagulability and bleeding time, blood chemistry, urinalysis and basal metabolism rate were unaffected by the prolonged use of the hormone Six of 17 regularly menstruating women did, however, experience a delay of one to three weeks in one menstrual cycle In a few the regular periods were excessive

The tendency of large doses of estrin to produce excessive uterine bleeding becomes a problem in the management of the climacteric syndrome of women who are menstruating excessively To such patients it is better judgment to administer small doses, such as one ampule of theelin in oil (200 to 300 rat units) every other day or emmenin orally in doses of 3 to 6 teaspoonfuls daily In the event of failure to control the constitutional symptoms, a more concentrated product, such as progynon-B, may be used The resulting aggravation of excessive bleeding, if it does occur, can be controlled by means of x-ray therapy of the ovaries However, care must always be exercised to eliminate the possible presence of fundal malignancy

With the use of huge doses (10,000 rat units hypodermically every fourth day), we were able to relieve the most serious symptoms of the menopause in the majority of our patients in the course of three weeks After this time, half the quantity usually maintained the patient in a comfortable state for another month This dose was then gradually decreased until the end of six months On reaching the stage of treatment when small doses, such as 1000 rat units every fourth day, were needed, oral administration then became more feasible and equally economical The oral administration of 600 rat units, in three divided doses daily, is equal in effectiveness to the hypodermic injection of 1000 rat units every fourth day This daily intake may then be gradually reduced

For the purpose of clinical study, we selected from our clinic and private practice a group of 33 patients presenting

climacteric symptoms bordering on involutional melancholia. In fact, 3 of the group had attempted suicide and 3 others were obsessed with the desire of self-destruction. For the sake of accuracy, we have eliminated from our study those who showed concomitantly evidence of organic diseases, such as cardiorenal vascular changes, anemia and pelvic lesions, as well as those who gave a history of antecedent nervous instability.

To insure cooperation and to prevent interruption of continuous treatment for a period of six or more months, no charge was made for either service or material in most instances. The latter was generously supplied by Drs Stragnell and Schwenk of the Schering Corporation.

Illustrative of the type of patients in this group of 33 is the following:

B S, aged forty-eight years, ceased to menstruate five years ago. Vertigo, palpitation, insomnia, finger paresthesia, flushes and cold sweats developed soon thereafter, increasing in intensity gradually. During the past three years she developed hiccough which is usually not attributable to the climacteric. The hiccough recurred frequently and persisted during day and night. While in our office the patient hiccupped every twenty minutes for a period of two hours. This symptom as well as the others were promptly relieved with the use of huge doses of estria.

The patients were given 10,000 rat units of progynon B every fourth day hypodermically. In the average, the major symptoms (flushes, cold sweats, insomnia and palpitation of the heart) subsided after the fifth or sixth injection of the hormone. The dose was then gradually reduced to 5000, 2500 and finally to 500 rat units. The system of gradually reducing the dose (without the patient's knowledge) was governed by the response to treatment. Often it was necessary to return to the use of maximal doses. The symptoms (mostly flushes, cold sweats and insomnia) of 2 of this group repeatedly reappeared as soon as the dose was reduced to less than 5000 rat units, even though they were not aware of the reduced dosage. They have been receiving this enormous quantity more or less regularly for nearly a year.

The length of treatment required to insure against a return of symptoms cannot be predicted in cases of severe climacteric manifestations, such as our group of 33 presented. The symptoms recurred and treatment had to be instituted again in every patient treated less than two months. Eleven remained symptom-free for periods averaging seven months after a course of treatment of two to six months. The remaining 22 are symptom-free but still under treatment. Six of these are satisfactorily maintained on very small doses administered orally. Four of the group of 22 under treatment for seven months still require 2000 to 5000 rat units every fourth day in order to prevent recurrence of the symptoms. It is interesting to note that not one of the 33 patients, regardless of the severity of the symptoms (whether neurocirculatory or mental), failed to respond to this treatment.

Judging by the length of treatment required, the administration of the hormone is largely substitutive. That this is not wholly the case is evident from its effectiveness in large doses in those who have a normal or nearly normal natural supply of the follicular hormone. In this class of patients, as shown by Kurzrok,² small doses are totally ineffective. It is our experience that large doses are no less effective in these patients than in those who show no estrin excretion. It is thus apparent that the hormone is not purely substitutive, since those who still produce a fair amount of it are equally benefited by its use in large doses.

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THE HOME TREATMENT OF PULMONARY TUBERCULOSIS

Each time that a physician makes a positive diagnosis of pulmonary tuberculosis he is immediately confronted with the problem of how is the best way to handle this individual patient. Too often the patient is told that he has a spot on his lung and should go away to a sanatorium or to the country and rest. This very casual method falls far short of the physician's duty to his patient. There is too great a tendency on the part of many physicians to neglect their responsibilities when dealing with tuberculosis. This lack of interest of the profession as a whole is probably due to the decrease in the death rate of the disease in the past few decades. In spite of the drop in the mortality rate, it should be borne in mind that there are from 75,000 to 80,000 new cases of pulmonary tuberculosis reported each year, and that tuberculosis stands first in destructive importance between the age groups of twenty and forty five. When a diagnosis of tuberculosis is made the patient and the patient's entire family are thrown into a state of upheaval, and for this reason it is too frequently made light of by the attending physician and the patient is allowed to drift along on inadequate treatment during which time the disease progresses. This to my mind is one of the most important reasons why well over 50 per cent of all patients admitted to sanatoria have far advanced disease at the

time of admission This manner of handling patients has done a great deal to discredit the value of home treatment of tuberculosis

The physician's first duty after making a positive diagnosis of pulmonary tuberculosis is to insist on absolute bed rest Rest is the foundation stone for the treatment of all pulmonary tuberculosis The family should be told the truth and in practically all instances, the patient Tuberculosis is a disease requiring months or even years of treatment and it is well for the patient and the patient's family to realize and face these facts early No intelligent individual can go through a cure for tuberculosis unless he is told the truth about his condition After the patient has adjusted himself, plans should be made for taking the cure, and we are faced with the problem of sanatorium treatment against home treatment Undoubtedly a number of factors will have a bearing on the final decision The easiest thing for the physician to do is to advise sanatorium treatment I know of no state that has sufficient beds available to care for every case of active disease Pennsylvania for instance has only 5260 beds, which includes private institutions During 1934 the death rate from pulmonary tuberculosis alone was 4291, for tuberculosis other than pulmonary 428 This means about 1.2 beds per tuberculosis death

Most states have between one and two beds per death per year, whereas it is estimated there are about ten cases of active disease for each death This is quite evident proof that there are not enough beds available for all patients and some will have to be treated at home It is quite true that sanatorium-treated patients as a whole are possibly better treated than the average home-treated patient This I believe in most instances is due to the apathetic manner that the patient is handled rather than to the method of treatment The most important factors in sanatorium treatment are

- 1 Medical supervision by a group of physicians, nurses and attendants specially trained in the care of tuberculosis
- 2 The education that a sanatorium patient gets about his

the reader that the convulsions can be controlled by the intravenous injection of soluble barbiturates (*c g*, sodium amytal in doses of 0.5 to 1 Gm.)

The rarely used drug picrotoxin, in poisonous doses, gives rise to clonic convulsions quite different from the tonic "spinal" convulsion of strychnine poisoning, poisoning by such common alkaloids as atropine and cocaine is marked by delirium, but rarely by convulsions

Lastly, hysteria is to be remembered as being capable of simulating any of the convulsive states mentioned above. Fortunately, the hysterical attack usually betrays its nature by bizarre features and a certain incompleteness of the picture, especially on close scrutiny of the circumstances of the seizures and of the background of the individual

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CLINIC OF DR. D. STEWART POLK

CHILDREN'S HOSPITAL

THE DIAGNOSIS AND TREATMENT OF CONVULSIONS IN CHILDREN

It is a commonplace observation that convulsions are more frequent among infants and young children than among adults. It is also generally agreed that young babies have seizures more often than do older children. Certainly the records of any hospital for children show a larger number of children admitted for the treatment of convulsions who are under three years of age than over three. Yet though young children have thus established a reputation for having convulsions more often than do older children or adults it is perhaps not admissible to assume therefrom that infants react convulsively to minor or unimportant causes. On the contrary it is well known that the peripheral nerves in young infants are definitely less irritable to the galvanic current than at later ages. Also relatively large amounts of fluid can be accommodated within the elastic skull of the infant without causing much damage. Moreover, experimental work on the nervous systems of animals shows that young animals regain their reflexes after severe injury much sooner than do adults of the same species. Crothers has come to the conclusion that the "newborn baby's nervous system will not respond convulsively to anything but gross insults."

Inasmuch as a generalized convulsion constitutes one of the most terrifying and one of the least understood symptoms in the whole realm of medicine it is highly important in the study and treatment of any person suffering from this symptom to approach the problem with the determination to find, if possible, the underlying cause. If we content ourselves with the

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thought that children are peculiarly susceptible to seizures because their brains are not fully myelinated, we shall some day overlook tetany or an early organic cerebral lesion, and we shall certainly not add anything of value to the knowledge of fundamental causes and mechanisms that produce the convulsion. We shall do better both for our patient and for medical progress if we study a convulsing child with this question dominating our thoughts. "What causes, physiological, pathological or pharmacological, underlie this remarkable set of symptoms?"

The analysis of a generalized convulsion is no mean test of an individual's powers of observation. The onset is sudden, often without warning and the phases of loss of consciousness, tonic contractions, twitchings, clonic jerkings—with the associated variations in pulse and respirations and the color changes from pallor through cyanosis to flushing and sweating—all these may transpire rapidly or comparatively slowly, the duration of any phase may vary in relation to the other phases and one or more of the steps may be apparently omitted altogether. Thus in infants we often see convulsions in which consciousness is apparently only clouded and where the motor phenomena are simply a few involuntary twitchings of the muscles of the extremities or the face. In jacksonian epilepsy repeated clonic movements of one small group of muscles may be the only external manifestations of a seizure, and of course in petit mal, a very short lapse of consciousness usually comprises the entire "spell." Much can be learned from the careful observation of the march of events in any convulsion, and detailed description thereof constitutes the cornerstone of the diagnosis.

The physical examination of a convulsing child should be as complete as the circumstances will allow, with the purpose in mind of establishing a working diagnosis as quickly as possible in order to start efficacious treatment promptly. Administration of ether or chloroform is often an immediate indication. When the convulsion is under control the examination is to be completed with special reference to the central nervous system, the peripheral nerves, the ears and sinuses,

the eyegrounds, and a routine survey of the other systems of the body. Urinalysis, blood count and spinal fluid study are the basic laboratory aids. Other procedures are carried out when indicated.

The history is taken from a general point of view with additional attention directed toward the record of the birth, the phenomena of the neonatal period, the details of the diet, the growth and development, illnesses and accidents, and especially any signs or symptoms referable to the central nervous system. A description of the first fit and all attendant circumstances and accompanying symptoms is followed by a chronological record of succeeding convulsions, and their variations, if any, from the initial seizure.

Having followed some such plan of gathering information concerning the patient one is in a position to diagnose the greater number of the cases of convulsions seen in children. Further search by laboratory and special clinical tests will discover fundamental causes in a few more of the cases. A varying percentage will remain as "convulsions of unknown cause."

The differential diagnosis of convulsions in children theoretically requires the consideration of at least half a hundred etiologic possibilities. For practical purposes, however, the various causes of seizures may be grouped according to the age of the patient so that the more probable conditions will be considered first.

EARLIEST INFANCY, BIRTH TO ONE MONTH OF AGE

Full term and prematurely born infants are considered together in this group, the latter showing a relatively higher incidence of convulsions than the former. Three pathological states are the chief causes of convulsions during the first month of life. They are, in order of importance: (1) Cerebral birth injuries, (2) congenital malformations of the brain and (3) acute infections.

Babies who have been subjected to the more difficult methods of delivery and especially premature infants with their thin elastic skulls and their fragile blood vessels are fre-

quent victims of intracranial hemorrhage from birth injury. When the injury is not so severe as to be immediately fatal, the child may be born deeply asphyxiated. Symptoms of birth injury may be present immediately after birth or may not appear for several days. Cyanosis, a tense fontanelle, cervical rigidity, feeble cry, irritability and failure to nurse are usually noted before convulsions are seen. Twitchings of muscles of the extremities or of the face often precede a generalized convulsion. The convulsive seizure may last for from a few seconds to several minutes and is often more intense on one side than on the other, indicating thus a more extensive lesion on one side of the brain than on the other. Opisthotonos is often present. Between seizures one or more of the extremities may be quite rigid. Respiration is irregular, usually slow. The pulse may be slow or rapid. Nystagmus is common.

Examination of the cerebrospinal fluid is an important aid in diagnosis. Lumbar puncture usually shows bloody spinal fluid containing crenated red blood cells, an excess of white blood cells and xanthochromia of the supernatant fluid if the lesion is some hours old. If the lesion is very recent xanthochromia and crenated cells will not be seen. A colorless fluid does not rule out intracranial injury for the lesion may be in the substance of the brain tissue, in the ventricles, or, rarely, epidural.

Treatment should aim at controlling further hemorrhage and at reducing increased intracranial pressure. The former may be accomplished by the intramuscular injection of citrated whole blood, 20 to 30 cc, or by a small transfusion of properly matched whole blood. Reduction of pressure is favored by repeated lumbar puncture. When symptoms indicate disturbance of the vital centers in the medulla, cisternal or ventricular puncture may be done, but great caution must be exercised to avoid injury by the needle to the medulla in the former case, or to the brain and choroid plexus in the latter case. Regardless of treatment a large majority of infants who show definite clinical signs of intracranial hemorrhage die within a few days.

Infants with congenital defects of the brain may show signs which simulate birth injury. Convulsions may or may not occur. Clear cases of microcephalus, hydrocephalus or mongolism are usually obvious in the early days of life. However, the diagnosis may be in doubt until the child has shown by its abnormal development that a deficiency or malformation of the brain exists. In general the presence of multiple abnormalities, such as congenital heart disease, spina bifida, etc., in association with evidences of cerebral dysfunction points toward the prenatal origin of all of the pathology. Early convulsions point to birth injury or meningeal hemorrhage. In Ford's series of congenital spastic palsies convulsions occurred at birth or during the first few weeks in 16 per cent. Relief of cerebrospinal fluid pressure and mild dehydration are desirable therapeutic measures. Sedative drugs such as chloral or phenobarbital may be used in small repeated doses, 1 grain of the former or $\frac{1}{12}$ to $\frac{1}{8}$ grain of the latter, but little improvement is to be expected in cases of organic brain pathology showing convulsions before one year of age.

Third in importance in causing convulsions during the first month of life is the group of acute infections. The umbilicus is to be thought of as the main portal of entry for infection from which septicemia may result. Erysipelas and tetanus neonatorum are to be borne in mind. The latter develops rapidly. The earliest symptom is difficulty in sucking due to trismus, but soon tonic contractions of the muscles are seen with cyanosis at first occurring spasmodically, but later almost continuously. The temperature is not always elevated, but is often high and irregular. If the child recovers the spasms gradually become less intense until they disappear within two or three weeks. The mortality is high, approximately 80 per cent.

The successful treatment of tetanus neonatorum requires relatively large doses of sedative drugs to control the spasms. The barbiturates, especially sodium phenobarbital and sodium amytal by hypodermic in doses of 1 grain may have to be given and perhaps repeated until anesthesia supervenes.

Tetanus antitoxin must be given in large doses, preceded by a skin test to determine the absence of sensitivity to horse serum. Ten thousand units may be given intramuscularly and an equal amount intravenously for three successive days. The intraspinal route is distinctly dangerous in infants.

Meningitis, due to congenital syphilis, is an important cause of convulsions in early infancy.

Meningitis, due to the meningococcus, pneumococcus, streptococcus, or influenza bacillus is rare in the first month, more common later.

Encephalitis also is more common in older children.

ONE TO FOUR MONTHS OF AGE

Convulsions associated with the toxemia and pyrexia of infections of the respiratory, gastro-intestinal, urinary or any other system of the body, are very frequent in children of all ages, but particularly so after the first month of life. In this age group the majority of convulsions result from the acute infections and fewer from the remaining birth injuries and congenital cerebral defects. Febrile disturbances of all sorts are frequently ushered in by convulsions, single or repeated. A convulsion indicating that the central nervous system is the seat of disease is more likely to occur as a later symptom. Thus in pneumonia convulsions at the onset are almost always of the toxic or febrile type, while convulsions late in the course of pneumonia are more likely to indicate meningitis of pneumococcal origin. The convulsions of pyrexia are, as a rule, transitory and not of grave significance and usually leave no tendency to suffer from repeated fits. The diagnosis of febrile convulsions depends on the presence of fever, general toxicity, and symptoms or signs of an acute infectious process, often as obvious as scarlet fever or tonsillitis, sometimes obscure. No organic nervous condition will be found and the seizures will disappear once the infection is on the wane.

The treatment is first directed at the seizure and, as a rule, simple measures are effective in bringing it to an end. Cold applications to the head with heat to the feet constitutes a time-

uremia. Any condition which causes obstruction in the urinary tract and back pressure upon the kidneys will, with comparative rapidity, produce uremia. Prostatic hypertrophy, urethral stricture, compression of the ureters by a pelvic tumor

It is clear that uremia is produced by retention of substances, mainly nitrogenous, which should have been excreted. Whether the familiar components of the nonprotein portion of the blood nitrogen—urea, the largest fraction, and after it creatinine and uric acid—are responsible, or whether some unidentified metabolites are more toxic, is not of great importance for our present purpose. The outstanding change in the blood in uremia is the increase in the blood urea, expressed as urea nitrogen, it often reaches 200 mg per 100 cc., and in true uremia is rarely if ever below 50 mg per 100 cc. Creatinine, uric acid, and total nonprotein nitrogen ordinarily roughly parallel in their increase the rise of the urea, amino acid and ammonia nitrogen are usually normal. The indican content of the blood is usually increased. The chlorides are low, probably from wastage of salt in the increased amount of dilute urine, and from persistent vomiting. Acidosis is usually present with great decrease in the carbon dioxide content of the plasma.

The patient suffering from true uremia exhibits the evidences of the condition which has produced the uremia. In the great majority of instances, this means the signs and symptoms of the late stage of chronic glomerulonephritis. Under-nutrition even emaciation, and the pallor of marked secondary anemia are usual. The pallor frequently is modified by a yellowish tinge without real jaundice. The frequently described 'urea frost' (deposition of fine crystals of sweat borne urea upon the skin) is, in the writer's experience, rare. The urinous odor of the breath, a traditional feature, is produced by bacterial decomposition of the increased salivary urea, but more often the breath is simply fetid, as in any chronic and severe illness in which cleanliness of the mouth is difficult for the nurse to maintain. The loss of appetite is often complete. Vomiting is almost invariable in occurrence, but highly vari-

able in frequency, it may be extreme. Diarrhea is common, and is likely to be produced by the "uremic ulceration" which may occur anywhere along the gastro-intestinal tract¹⁵. The circulatory symptoms depend for the most part upon the presence or absence of myocardial exhaustion and failure in conjunction with long-continued hypertension, ordinarily not very prominent, in some instances dyspnea, orthopnea, and palpitation may be as marked as in congestive heart failure from valvular lesions. The blood pressure is ordinarily high, both the systolic and the diastolic, not infrequently, it may be found to be normal or low because the myocardium no longer has sufficient strength to maintain a high pressure. "Uremic pericarditis" is common, often detected only by the accidental finding of a pericardial friction, rarely accompanied by effusion, usually surprisingly painless, and almost always a terminal event. In addition to the dyspnea of circulatory weakness, acidosis may produce exaggerated breathing of the Kussmaul type. The skin and mucous membranes not infrequently exhibit various purpuric manifestations.

It is to be emphasized that convulsions are not prominently a part of the symptom-complex of true anemia. If they occur at all, it is likely to be in the last few days of life, after many other features have clearly indicated that the fatal termination is at hand, if they occur, they are generalized and epileptiform. Restless physical activity, semi-involuntary and semipurposeless, is, however, usually seen. The patient tosses and turns in bed, he picks his nose, or scratches, or picks at the bedclothes. Involuntary twitchings of large or small groups of muscles, and coarse tremors of the fingers and limbs, are usual. The mental state is marked by apathy and confusion, and the patient may remain semiconscious for many days.

Pseudo-uremia, or acute eclamptic uremia, on the other hand, consists of convulsive seizures occurring in the course of nephritis, either acute or the chronic glomerular variety, or of some other hypertensive syndrome. Fishberg¹⁰ stresses the observation that arterial hypertension is the essential feature, and prefers the term "hypertensive encephalopathy" for this

type of convulsions. The disturbance responsible for the actual production of the convulsion appears to be edema of the brain, or vascular spasm affecting the arterioles of the brain, or a combination of the two. Failure of renal function and retention of excretory products are assuredly not responsible, for the syndrome occurs when the chemical composition of the blood is unaltered.

The convulsions are best described as being epileptiform, that is, they are usually generalized, are clonic, are customarily followed by unconsciousness and are sometimes preceded by warning symptoms such as paresthesias or severe headache. Variants are described, such as unilateral or jacksonian convulsions, but these are rare. The convulsive seizure may be a comparatively isolated episode, not to be repeated for a long time, or the fits may recur at short intervals.

In general, the occurrence of pseudo-uremic convulsions indicate a sufficiently severe disease to render the eventual prognosis grave. An exception to this is in cases of acute nephritis, particularly in young persons, where after recovery from the disease of the kidneys the blood pressure subsides to normal. A series of rapidly repeated convulsions is likely to end in death from exhaustion.

The treatment of true uremia is that of chronic glomerulonephritis—too extensive a subject to review here. The aim of such treatment is to ward off uremia, and by the time the stage of uremia is reached in spite of careful management, palliation of distressing symptoms is as much as can be hoped for. Mention may be made of a few considerations. Adequate intake of fluid, salt, and glucose should be maintained, diarrhea need not be checked unless excessive, if there should be constipation vegetable cathartics are usually preferable to saline, sodium bicarbonate will give transient relief of acidosis and its symptoms, sedatives are indispensable because of the patient's distress, any sedative may be used, but morphine or dilaudid may eventually prove the most effectual, and one need not fear an ill effect upon the kidneys. Venesection is useless, and in dialysis usually contraindicated because of the degree of anemia.

Sweating, in this stage, is usually both useless and inadvisable because debilitating

Probably more applicable to the preuremic stage of nephritis than to the uremic are a few therapeutic suggestions which have been made recently. Schwarzmann,¹⁷ of Odessa, obtained improvement by means of injections of a tissue extract prepared from skin, pleura and lungs. By section of renal nerves, Rieder¹⁸ produced renal vasodilation and clinical improvement in 1 case. Tixier and Eck,¹⁰ of Paris, have used an extract of artichoke, by injection, and in several cases produced an increase in urinary nitrogen excretion and a fall of the nonprotein nitrogen of the blood. The writer has had no experience with these modes of treatment, and mentions them only as tentative and unproved methods.

The treatment of the fit in pseudo-uremia or hypertensive encephalopathy is a matter of great importance, it is often possible to change a bad prognosis to one which is at least temporarily good. Two measures are of outstanding value, venesection and lumbar puncture.

If a prodromal stage, indicated by such symptoms as severe headache, disturbances of vision, or paresthesias, is recognizable, venesection done then may prevent the occurrence of the convulsion. After convulsions have occurred, venesection appears to diminish the chance of their recurrence, and to lessen the duration of coma. The venesection should be free—400 or 500 cc. Removal of blood should be rapid, by cutting down on the vein, or by using a large needle such as is used for transfusion donors, possibly with a suction apparatus such as the Potain aspirator, the speed of withdrawal of blood appears to influence the therapeutic result. Needless to say, such a venesection cannot be repeated frequently. The reason for the benefit produced is obscure, for the fall in arterial pressure may be slight and is almost invariably transient.

Lumbar puncture would seem to act beneficially by reducing intracranial tension, for the cerebrospinal fluid is often under increased pressure. However, the pressure of the fluid may be normal, and the puncture be followed by improvement.

nevertheless The puncture should be made cautiously and the fluid withdrawn slowly, the fluid may be allowed to drop slowly until its pressure, measured by a manometer, has been reduced to the normal level The puncture may be repeated two or three times in twenty-four hours if it seems necessary Other dehydrating measures may aid in lessening cerebral edema Retention enemata of hypertonic (50 per cent) solution of magnesium sulphate, or intravenous injection of 50 cc. of 50 per cent glucose solution Moderately free catharsis is desirable, but violent purgation is inadvisable. Sweating is useless

Sedatives are usually necessary Chloroform, given by inhalation to control convulsions, is a traditional resource, but is very rarely needed Chloral hydrate and the bromides are effective in many instances, and may be given by rectum Several of the comparatively new barbiturates (*e g*, sodium amytal) may be given either by mouth or by intravenous injection, according to the urgency of the indication, and can be made to control convulsions in the majority of instances. Caution should be exercised in the use of these barbiturates, because of their toxicity and the fairly frequent occurrence of idiosyncrasy In some cases, morphine, alone or with hyoscine, may be the most effective sedative.

Tetany, while not attended by generalized convulsions, is at least a convulsive state, and is manifested by localized convulsions Its principal occurrence is in children and it is a matter of great importance to pediatricians Tetany in adults occurs under comparatively few circumstances, chief of which is the accidental ablation or injury of the parathyroid glands in the course of operations upon the thyroid gland

The characteristic phenomenon of tetany is the carpopedal spasm, which consists of strong adduction of the thumb, flexion of the fingers at the metacarpophalangeal joints, and plantar flexion of the feet Spasmodic flexion at the wrist and elbow also may occur Laryngeal spasm is not a prominent feature of tetany in adults. The muscular spasms give rise to severe pain "Latent" tetany is disclosed, readily in most instances, by two principal physical signs or by characteristic changes in the

electrical excitability of peripheral nerves Chvostek's sign is a twitch of the muscles of the angle of the mouth, the ala nasi, and the eyelids, following a sharp tap over the facial nerve below the zygoma Trousseau's sign is elicited by making firm pressure (a little above the individual's systolic blood pressure) about the upper arm by means of a tourniquet or the cuff of a blood pressure instrument, and maintaining the pressure from three to five minutes, in the presence of tetany, the carpal spasm is produced on the compressed side In hypoparathyroid tetany, the one constant laboratory finding is the diminution of the total calcium of the blood serum to 7 mg per 100 cc or less

Tetany from functional hypo-activity of the parathyroid glands (a theoretical syndrome comparable to myxedema) has not been described However, disturbances of parathyroid function probably play a part in the tetany occasionally seen in association with cretinism and with thyrotoxicosis In the tetany of pregnancy and lactation, calcium wastage and parathyroid dysfunction are probably cooperating factors

"Gastric" tetany develops especially in cases of pyloric or high intestinal obstruction with persistent vomiting A definite and rather remarkable clinical picture is produced in these cases Toxemia, diminution of blood chloride (from loss of hydrochloric acid and chloride in the vomitus), alkalosis (evidenced by increased carbon dioxide content of the plasma), ketonuria, azotemia The tetany may or may not be produced, if so, the blood calcium content is not reduced The symptoms are readily relieved by supplying sodium chloride by means of intravenous infusion Alkalosis and tetany occasionally result from overdosage of alkalis in peptic ulcer

"Hyperventilation tetany" results from greatly increased respiration (e g, in hysteria or in severe fright), rapid elimination of carbon dioxide from the blood, and consequent alkalosis, there is no lowering of blood calcium This form of adult tetany has little clinical importance, provided only it is recognized when it occurs, and does not give rise to erroneous diagnosis and needless treatment Wilder has recently reported

hyperventilation tetany in a case of "spontaneous" hypoglycemia.²⁰

Acute hypoparathyroid tetany is usually promptly relieved by the intravenous injection of 0.5 to 1.5 Gm. of calcium chloride in 5 to 10 per cent solution, parathyroid hormone ("parathormone") may in addition be given by subcutaneous injection, or for more rapid effect, intravenously.²¹ Such patients may be kept in comparative comfort almost indefinitely by oral administration of calcium, and daily injections of parathormone. The dosage of the latter, like the dosage of insulin in diabetes, must be adjusted to individual requirements, the level of the serum calcium serves as a guide. In some mild cases the patient may be kept comfortable by oral administration of calcium alone. The writer prefers calcium gluconate, in the form of a fine powder, to the chloride or the lactate for oral administration; it seems to be easier to take and less irritating to the stomach, the daily dose ranges from 10 to 30 Gm. Surgical transplantation of human parathyroid tissue is a therapeutic possibility in severe and persistent cases.

Heart block exemplifies a circulatory disease, other than intracranial, in which convulsions and unconsciousness may occur. The convulsive seizures (Stokes Adams attacks) take place when there is a change from partial auriculoventricular block to complete block, and the ventricles, deprived of their customary impulse to contraction, stand still for several seconds before taking up their independent rhythm, with the resumption of ventricular activity circulation is restored, and rapid return of consciousness ensues. Anoxemia of the brain is the direct cause of the unconsciousness and convulsions.

Unconsciousness is a more prominent feature of the attack than convulsions, which usually consist of clonic contractions of the muscles of the face and upper extremities, in severe attacks the convulsions may become generalized. The attacks may occur only at long intervals, or they may be repeated every few minutes for many hours. In many cases, the heart block eventually becomes permanently complete, when this transpires the Stokes Adams attacks usually, but not invariably

ably, cease It is possible for a patient to live in fair comfort for several years with complete auriculoventricular block

The individual with partial heartblock and Stokes-Adams attacks presents evidence of underlying myocardial disease, usually sclerotic, not infrequently syphilitic, his treatment and management are those appropriate to the condition The attacks themselves terminate spontaneously in a few seconds, or they prove fatal, there is little opportunity for treatment Neither is there any satisfactory means of preventing the change in cardiac rhythm and thus preventing the attacks^{22 23} Theoretically it might seem that digitalis might be used in full dosage to render the auriculoventricular block complete and maintain it so, thus relieving the patient of attacks The writer has not had occasion to try this, and Wolferth²⁴ has stated that in practice it does not work out satisfactorily

Cerebral anoxemia from any cause, if severe and rapidly induced, is capable of producing convulsions A few convulsive movements are occasionally seen in simple syncope

Acute alcoholism, especially when prolonged, may be marked by epileptiform convulsions which readily give rise to errors in diagnosis Arnett²⁵ reports convulsions in nearly 3 per cent of a series of cases of alcoholism, in his group delirium tremens was usually absent, there were no deaths, and the convulsions were sometimes unilateral Edema of the brain is the probable mechanism of production of convulsions, it would seem probable that hypertension and cerebral arteriosclerosis are often factors Lumbar puncture is valuable in treatment, other measures appropriate are the restriction of fluid intake, the free use of saline cathartics, and perhaps intravenous injection of hypertonic (50 per cent) glucose solution

Strychnine poisoning in adults is surprisingly rare in view of the ease with which pellets of the drug may be purchased over the drug store counter, and in comparison with its relative commonness in children The diagnosis files of the Hospital of the University of Pennsylvania for the past nine years do not show a single admission to the medical division for strychnine poisoning It is mentioned here only to remind

honored ritual. When fever is high a cool or tepid sponge is a useful variation. A cleansing enema, preferably of sufficient saline to irrigate the lower bowel thoroughly, will often reduce temperature and remove an important source of irritation. The bowel is now prepared for a rectal administration of chloral hydrate 2 to 3 grains or sodium phenobarbital $\frac{1}{4}$ to $\frac{1}{2}$ grain, injected high into the bowel and prevented from escaping by pressing the buttocks together. If the seizure continues a few whiffs of ether or chloroform may be given to control the spasms temporarily. The rectal medication may be expected to take effect within twenty or thirty minutes, it may be repeated in one hour if necessary. If seizures recur in spite of these methods, sodium phenobarbital $\frac{1}{4}$ grain, or morphine by hypodermic $\frac{1}{80}$ to $\frac{1}{100}$ grain may be given provided respiration is not already depressed. Magnesium sulphate in sterile 10 to 20 per cent solution may be injected intramuscularly in doses of 0.3 to 0.6 Gm. for its sedative effect on the nervous system. Magnesium sulphate is useful, also, by mouth or stomach tube as a hydrogogue cathartic, thereby promoting dehydration and lessening intracranial pressure. If these measures fail, oxygen or O_2 - CO_2 inhalations may succeed and should always be used when cyanosis is marked.

Mild sedative action should be continued for two or three days after a severe bout of convulsions by the administration of chloral and bromide, or one of the barbiturates in small and gradually decreasing dosage. As soon as the convulsions have ceased the underlying cause should be sought and treated. The opening of a bulging ear drum or the reduction of fever by sponging may have a promptly beneficial effect on the course of the illness.

met occasionally as a cause of convulsions in infants under four months of age. Thus tuberculous meningitis, meningococcus meningitis and encephalitis may be found in young infants. Diagnosis depends upon thorough physical examination and spinal fluid studies. Treatment is that appropriate to the condition.

Any condition which produces anoxemia or marked cyanosis in young children is likely to precipitate a convulsion. Thus congenital heart disease with cyanosis, spasm of the larynx, laryngitis, tracheal compression, congenital atelectasis, pertussis and breath-holding spells, all are found producing deep cyanosis accompanied by convulsions.

A considerable residue of cerebral birth injuries and congenital defects will still be found as causes of convulsions. Hydrocephalus becomes a more frequent finding due to the gradual increase in the quantity and pressure of the cerebrospinal fluid within the skull as time goes on. The enlarged head, wide fontanelles and sutures and the retarded mentality make the well-developed case unmistakable, but there are milder cases showing only slight enlargement of the skull in which the true explanation awaits a ventriculogram, or the test of time. Rapidity of growth of the head is as important for diagnosis as is the fact of enlargement. Surgical treatment is very dangerous, medical treatment is usually unavailing. Limitation of fluids may be advised but without much hope of effect. A few cases become arrested spontaneously with only moderate mental deterioration, most die within the first year.

FOUR MONTHS TO TWO YEARS OF AGE

Spasmophilia, or infantile tetany, a condition of hyperirritability of the nervous system to mechanical and electrical stimulation is rare before the third month of life, but relatively common and exceedingly important as a cause of convulsions during the remainder of the first year and the whole of the second year. Hess said, "In its mildest forms tetany ranks among the disorders of infancy which most often pass unsuspected." Tetany may occur in a number of conditions when

there is loss of gastric secretion, alkalization of the body by the administration of excessive alkali disturbance of the parathyroid gland secretion, etc., but the overwhelming majority of the cases of tetany in childhood are due to rickets. Rickets can be demonstrated either clinically or roentgenologically in practically every case of infantile tetany.

The symptoms of tetany are not manifest except in those cases where the blood serum calcium content is below the normal level of 9 to 11 mg per 100 cc of serum. A serum calcium of less than 8 mg is characteristic of tetany. Serum phosphorus is often somewhat increased.

The characteristic physical sign of tetany is carpopedal spasm. It may come on spontaneously but often is precipitated by fever. It is frequently accompanied by spasm of the glottis, or laryngospasm, often severe enough to arrest respiration temporarily to produce cyanosis and sometimes to precipitate a convulsion. Other easily detected manifestations of tetany are Chvostek's sign (hyperirritability of the facial nerve to mechanical stimulation) and the peroneal sign (dorsi flexion and abduction of the foot on tapping over the peroneal nerve). Erb's sign (increased excitability of the peripheral nerves to the galvanic current) requires a galvanic battery and a milliammeter. The presence of these signs in a child whose serum calcium is less than 8 mg per 100 cc serum constitutes a diagnosis of tetany. Generalized convulsions may or may not occur. They are more common during the first year than later. They are almost always bilateral, may be mild or severe, are of short duration, but tend to recur until treatment is effective. The treatment of the convulsions of tetany consists in the use of the usual measures for the control of convulsions with in addition the administration of calcium to prevent further seizures, and antirachitic therapy to remove the underlying metabolic disturbance.

Calcium may be given in the form of a 10 per cent sterile solution of calcium gluconate either intramuscularly or intravenously with rapid absorption and effect. Three or 4 may be necessary before the convulsions cease.

chloride may then be given in a 10 per cent solution by mouth, 1 Gm every four hours for the first day, thereafter reducing the dose to 1 Gm three times daily. When the serum calcium reaches 9 or more milligrams convulsions will no longer occur.

Antirachitic therapy should not be started until calcium has been given for at least twenty-four hours since the blood calcium may fall to new low levels owing to increased calcium deposition in the bones. After an excess of calcium has been supplied for a day or two, vitamin D is indicated in curative doses. Viosterol 250 D, 20 to 30 drops a day, or its equivalent, should be given until the lowered blood calcium and all other signs of rickets and tetany have disappeared. A dose of 10 to 15 drops a day will usually suffice to prevent recurrence of rickets or tetany. Direct and regular exposure of the skin to sunlight or to an artificial source of ultraviolet light is valuable prophylaxis against rickets and tetany during the warmer half of the year, but is of no practical value during the cold months.

AGES TWO TO SIX YEARS

As the tetany age is outgrown other factors crop up more frequently as causes of convulsions. Poisoning with convulsant drugs is seen more often in run-about children of preschool age than in any other group. In fact deaths from strychnine poisoning are in excess of deaths from tetanus and rabies combined. Sugar- and chocolate-coated cathartic tablets containing from $\frac{1}{60}$ to $\frac{1}{120}$ grain of strychnine have often tempted children by their candy-like appearance and taste and when swallowed in considerable numbers have promptly led to strychnine poisoning with convulsions and death. Such tablets may be bought without prescription, are not labelled "poison" and are not ordinarily considered dangerous. Strychnine poisoning is acute. Symptoms appear within an hour after ingestion. Clonic spasms begin in the fingers and hands and soon become tonic with opisthotonos. Consciousness is not lost at any time. The tonic spasms recur with increasing severity, but in the intermissions, which last for several minutes, the muscles

are completely relaxed. The slightest external stimulation, even a light touch, is likely to set off another violent spasm. If the convulsions cannot be controlled, death will soon follow from respiratory paralysis and exhaustion.

Treatment is similar to that of tetanus convulsions in that large doses of sedative drugs are necessary. Sodium phenobarbital or sodium amytal are the drugs of choice and should be given to the point of anesthesia and depression of the respiratory rate. If a Drinker respirator is available it should be used when cyanosis appears. The prognosis is good if the child survives the first six hours.

Lead poisoning is by no means rare in childhood. It is usually due to paint eating and is most common between the ages of two and five years. A child may in the course of several weeks gnaw a considerable quantity of paint from his crib and toys. Lead poisoning is cumulative, not acute. Symptoms develop insidiously and the early pallor, listlessness, anorexia and constipation may not be considered important until cerebral symptoms make their appearance. Encephalopathy is very frequent and is usually manifested by severe convulsions. They often occur in series and are exceedingly difficult to control with ordinary sedatives. Lumbar puncture yields fluid showing few cells, markedly increased globulin content and increased pressure. When lead poisoning is suspected in a child a search is made for a history of contact and for five special signs, namely: anemia, basophilic stippling of the erythrocytes, a lead line on the gums, characteristic shadows in the x-ray films of the long bones and the presence of lead in the circulating blood as determined by the spectrocope. The two latter are the most reliable criteria and deserve a few words of explanation since they are quite recent discoveries. In a child suffering from lead poisoning, x-ray films show dense transverse shadows at the shaft-epiphyseal junctions in the long bones, as the child grows the shadow remains where it was and new bone is added at the end of the shaft normal in density if exposure to lead has ceased, and of increased density if further ingestion of lead occurs. The

in a child who has had two periods of lead absorption, separated by an interval of no absorption, a double transverse shadow will be seen in the x -ray pictures, one band a short distance from the end of the bone, the other at the junction of shaft and growing cartilage. In some cases the shadows are only suggestive of lead poisoning, but in others they are so characteristic as to make lead poisoning almost a certainty. The spectroscopic test for lead in the circulating blood is very sensitive. It requires an expensive instrument and unusual technical assistance and is not as yet generally available. A negative spectrogram rules out lead poisoning, a positive indicates that lead is circulating in the blood and may be the cause of the symptoms in question. The prognosis of children with encephalopathy is very poor, the majority of the cases die, of those who recover most have permanent mental deficiencies.

Treatment is similar to that of strychnine poisoning. In addition to heavy doses of sedative drugs, lumbar puncture or decompression by craniotomy is useful by relieving the increased cerebrospinal fluid pressure. In a few cases continuous spinal fluid drainage has given good results. After the signs of encephalopathy have subsided the use of sodium acid phosphate, 15 grains, *t i d* in a six-year-old child, with a high phosphorus low calcium diet aids gradual removal of the lead from the body in the form of insoluble lead phosphate.

Another important cause of convulsions in children past the age of infancy is uremic poisoning. It occurs early in a considerable number of cases of acute nephritis and is the usual termination in chronic nephritis. The signs of nephritis, including a systolic blood pressure of 140 to 180 mm, are always present when uremia is the cause of seizures. In treatment chloral and morphine are highly recommended. Magnesium sulphate in large doses by mouth is of great value. Its cathartic effect is less than in well children. Magnesium sulphate may also be given intramuscularly in 10 per cent or intravenously in 1 per cent solution up to a total dose of 0.1 Gm per kilogram of body weight for its antispasmodic and spinal

pressure reducing action (Uremia is discussed in more detail by Dr Cottrell in this number of the Medical Clinics)

To complete the list of poisons likely to produce convulsions one must consider carbon monoxide inhalation and the rare cases of poisoning by cocaine, camphor, caffeine, ergot, and a few other drugs hardly ever met with in practice. Hypoglycemia, either spontaneous or insulin induced, is usually accompanied by convulsions when the blood sugar level falls below 50 mg per 100 cc of blood. Pallor, a cool moist skin, extreme weakness, and often vomiting precede the muscular spasms. If untreated many of these seizures will pass off spontaneously, but the situation is potentially dangerous and the administration of glucose by mouth or parenterally is urgently indicated and promptly effective. Encephalitis, presumably caused by one of a number of neurotropic viruses, is not to be overlooked in children showing convulsions in combination with symptoms suggesting cerebral and cranial nerve pathology. It may appear apparently spontaneously as epidemic encephalitis. Other forms are secondary to certain virus diseases, especially smallpox, varicella, measles, mumps and chickenpox. Pertussis is also a frequent cause of convulsions and other profound nervous disturbances. Treatment of the symptoms of encephalitis is symptomatic. Convalescent serum is theoretically of value and should be given. Rabies is a rare condition to be differentiated from tetanus by the history of a bite by a rabid animal, by the intense mental excitement, the pharyngeal and laryngeal spasm and the increased spinal fluid cell count. Once established rabies invariably kills. Sedatives and anesthetics should be given freely.

SIX TO SIXTEEN YEARS OF AGE

After the sixth year of life idiopathic epilepsy is found as the most frequent cause of convulsive seizures in children. Only a few cases seem to be clearly established at three years of age. Idiopathic epilepsy is a convulsive state for which no organic or physiologic basis has as yet been demonstrated.

The diagnosis is to be made after only the most thorough search has failed to reveal any organic or extrinsic factors that could produce recurring attacks of unconsciousness with or without muscular contractions. In the convulsions of idiopathic epilepsy, loss of consciousness is the fundamental clinical phenomenon. Momentary lapses of consciousness without muscular spasms (*petit mal*) may be the only symptom seen for years but gradually these cases develop the additional motor phenomena which characterize the major fit (*grand mal*). Aurae are rare in children, the fit starts usually without warning. Suddenly consciousness fails and the patient falls if not supported. All voluntary muscles including those of respiration become rigid. The lips and face become pale, then cyanosed. The pupils dilate, become fixed, gradually the muscles begin to jerk, rapidly at first then more slowly and with greater range. The eyes jerk to the side of greater spasm and the pupils contract. Air enters the lungs again as short sobbing breaths are taken and froth, often blood-stained, issues from the lips. Cyanosis gradually fades and flushing may appear. Micturition and defecation mark the more severe seizures. As movements cease, coma remains with stentorous breathing, flaccid limbs and profuse sweating. A few minutes later coma passes into natural sleep or the child awakes perhaps with a headache or partially exhausted. Epileptic fits are more frequent at night than during the day and some children go for years with no day time but many night time attacks. Often the only signs that a convulsion has occurred are a bitten tongue and a blood-stained pillow in the morning. The child may have been unaware of his experience.

Hysterical convulsions, rare in children, are distinguished by a preliminary emotional upset, the presence of an audience, failure to fully lose consciousness, a natural color, never cyanosis, eyes tightly closed and resistant to opening and a general tremor followed by purposive movements.

Jacksonian, or epileptiform, seizures are focal in nature and indicative of organic disease affecting a relatively small part of the brain. They characteristically start as twitching of

a single muscle or extremity and gradually spread to involve the whole body. Consciousness is lost late or not at all. The lesion in the central nervous system may be a depressed skull fragment, a thickening or adhesion of the meninges, an abscess, a tumor or other lesion, irritating the cortex of the brain. A complete neurological examination including x ray of the skull and ventriculogram, may be necessary to localize the lesion.

During an epileptic seizure the patient should be protected against bodily injury. He is safest lying on the floor or on the bed with a soft support for his head. A soft wood or rubber wedge will prevent tongue biting. Gentle restraint is usually necessary for only a short time as most fits are over within from three to five minutes. Repeated severe convulsions occurring at short intervals without the regaining of consciousness between attacks (status epilepticus) are undoubtedly harmful and even dangerous to life. Ether or chloroform inhalations are useful at first but should be quickly followed by sodium phenobarbital intramuscularly or intravenously from 2 to 8 grains according to age. Lumbar puncture with drainage of a considerable quantity of spinal fluid is a helpful move. Inhalations of 90 per cent oxygen and 10 per cent carbon dioxide helps to promote normal respiration and relieve anoxemia. Finally magnesium sulphate solution by mouth for its dehydrating effect or urea 10 to 15 Gm every six hours for its diuretic effect may be helpful. When the seizures cease, fasting or feeding of cream oil or butter will promote a desirable acidosis and prepare the way for the ketogenic regime.

Between the convulsions the treatment of epilepsy consists in attempting to decrease the irritability of the cells of the central nervous system. Sources of chronic or acute irritations such as focal infection, bad habits or even mental stresses or strains are sought out and removed. Good physical hygiene is fundamentally important. Life should be regular, rest, work and play are to be well balanced. Outdoor exercise in moderation is particularly valuable. Overexertion, especially at night is to be avoided. Just as fundamentally im-

portant is good mental hygiene. Mental stresses, many of which may not be obvious to the patient or to those associated with him must be removed. Anxiety over school work, emotional conflict with a parent, or the disdainful attitude of the public at large may account for a child's failure to respond well to treatment. So far as possible his environment and activities should be those arranged for the normal child. The drug treatment of epileptic children between seizures is of value as a temporary expedient and in some cases seems to break the cycle of recurrent seizures for a considerable length of time. Bromide, either a sodium, potassium or ammonium salt, should be given in sufficient quantity—10 or 16 grains a day for a child of ten years—to establish and maintain a level of bromide in the blood of about 150 mg per 100 cc. Definite lessening of the frequency of seizures is to be expected while this level is maintained, but if the drug is omitted for several days, convulsions sometimes occur in excessive numbers. Unpleasant by-effects of bromides are seen in certain patients. Simple hebétude is the most common complaint. Violent mental disturbances have occasionally been seen early and late in the course of bromide therapy. Other patients show characteristic bromide acne, intestinal disturbances and at times marked somnolence.

Phenobarbital has been found by most clinicians to be more satisfactory than bromide, $\frac{1}{2}$ grain three or four times a day, best prescribed as the sodium salt in solution, is an average dose for a ten-year-old child. It may be divided so that most of the medication is given shortly before the time when seizures usually occur. Phenobarbital is often very successful while in constant use but if discontinued suddenly, a flood of convulsions is likely to ensue. When it becomes desirable to discontinue phenobarbital the dose should be reduced gradually. The borotartrates have been used by relatively few observers and opinion is still divided as to their efficacy. When used in combination with bromide, borotartrate has seemed to heighten the anticonvulsive effect and at the same time to lessen the mental depression that so often results from bromide alone. The dose is the same as that for bromide.

Drug treatment is at best a temporary expedient and not a curative agent. Moreover the disadvantages of the continued use of sedatives are particularly serious in children. Mental deterioration is sometimes seen when sedative drugs are given over a long period of time. Fortunately, a more promising therapeutic measure is available in the ketogenic diet. This is particularly applicable to children and is more effective the earlier in the course of the epilepsy it is begun. In a large series of epileptic children Helmholz reports 57 per cent either well or improved and 43 per cent not benefited. Where the children are studied most thoroughly and those with fixed lesions of the brain are excluded the results of the dietary regime are distinctly more favorable. Thus Eley did preliminary encephalograms on his convulsive cases and found that 90 per cent of the cases showing normal encephalograms responded favorably to the ketogenic diet, while only 12 per cent of those showing abnormalities improved under treatment. The ketogenic diet is best initiated following a fast of from three to five days. Distilled water in moderate quantities and chewing gum are supplied to the child during this period. There is a prompt loss of weight effected chiefly by the excretion of water and electrolytes and coincidentally there develops an accumulation of ketone bodies in the blood and the appearance of acetone and diacetic acid in the urine. If a patient does not respond to fasting by a cessation of seizures it is unlikely that he will be much benefited by the ketogenic diet. On the contrary if the response is favorable the fast is terminated by putting the child on a diet in which the ratio of grams of fat to grams of protein and carbohydrate combined varies between 4 to 1 and $2\frac{1}{2}$ to 1. It has been found useful to restrict fluid intake at the same time in order to aid the dehydrating effect of the diet. To obtain maximum effects from the diet alone it is necessary to maintain a continuous acidosis indicated by strongly positive tests for acetone and diacetic acid in the urine. It is usually best to start with a diet ratio $\frac{k}{p+c} = \frac{1\frac{1}{2}}{1}$ and to lower the $\frac{k}{p+c}$ ratio only when it is clear that seizures have been controlled.

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for many months. The change is to be made very gradually and ketosis is to be maintained for as long as there is reason to fear a return of convulsions. Both major and minor epileptic seizures may be expected to benefit by the diet. When it has been decided to use a ketogenic diet for a considerable time it is important to calculate most carefully for all the essential food requirements of the child. Adequate food materials for growth and energy will be provided for a ten-year-old child when the diet contains 1.5 Gm of proteins and 0.5 Gm carbohydrate per kilogram expectant body weight and sufficient fat to make up a total caloric value of from 50 to 60 calories per kilogram expectant body weight. The total calories supplied may be varied with the condition of nutrition, the rate of gain in weight, the amount of exercise regularly taken and the climate. Sufficient minerals, especially calcium, must be provided. It is often desirable to add calcium to the diet in the form of calcium chloride or casein powder. The food should be weighed accurately until improvement is established, then careful measuring may be substituted for weighing. Meals should be as varied and as attractive as possible. The dietary regimen may be supplemented by restriction of the intake of salt and water in order to further favor dehydration, in the more difficult cases small doses of phenobarbital are often very helpful. No case should be considered uncontrollable until a combination of all of the more appropriate measures has been tried. Finally, one should not forget that in the treatment of convulsions, epileptic and nonepileptic, the golden opportunity is at the beginning of the illness. Prompt discovery of the cause and skilful execution of treatment will gain many splendid successes, delay will often end in tragedy.

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UNSATISFACTORY INTERCOURSE, ITS TREATMENT

It may seem amazing that there should be a real need for a paper of this title, but the mere fact that the "freudian school" of psychiatry has become so universally accepted as having a real value, indicates the necessity for a discussion of this topic. My own experience as a physician convinces me that there is a very real need for the doctor to discuss sex matters with his patients and that by failing to do so one not only neglects opportunities to be of great service but is often apt to misinterpret other symptoms. I think a fair definition of unsatisfactory intercourse would be sexual union in which one of the partners usually the woman, always or almost always, fails to experience orgasm. Such a definition would apply to a group of patients which is appallingly large, and for whom much can be accomplished.

Before embarking upon this topic, let me consider for a moment intercourse that is actually painful. One does see not infrequently, patients with this complaint. They are usually brides whose marriages have only been of a few days' or weeks' duration. The cure in most instances is easily effected by incising the fibrous hymen under local anesthesia, or by rapid digital stretching. It is fairly obvious that painful intercourse is rarely a fixed complaint for the reason that if the usual form of sexual union persists in being acutely painful to either partner, such relationship is not continued and some other form of sex expression not painful is substituted. Such cases, however, do occur.

Noble, in a recent report, describes a case of intense dyspareunia occasioned by reflex muscle spasm, with violent defense reactions of twenty years' standing, in which he was able to effect a dramatic cure by suggestion only. By the use of great tact and patience, he convinced his patient that the intense pain she experienced, the anticipation of which caused her to literally fight like a wildcat, was due to the spasm of her own muscles. He showed her that it was her own mental state and not her husband's actions, which was responsible for the spasm. He convinced her that if she herself would take the initiative in sex relations, it would insure her own proper preparation for coitus, and that so prepared the spasm with its attending pain could not occur. The consideration of such isolated cases are of great value, inasmuch as the principles involved in treatment are exactly the same as those utilized in handling that exceedingly common condition, unsatisfactory intercourse.

It is my hope to point out in this paper, particularly to the general practitioner and the obstetrician, that a tremendous opportunity to be of incalculable assistance to his patients is ever present, waiting to be grasped, if he will only take the initiative in the matter. It is my impression that certainly one out of every four of the patients, both ward and private, that I see at their sixth week postpartum visit, have not been having satisfactory sex relations. Only a few of these patients are real psychiatric problems. I refer to those unfortunate individuals who are born with a nervous system unable to meet the demands that life makes upon it, who never could or can adapt themselves to their environment, and whose emotional life is a constant series of inhibitions and "escape mechanisms." Little can be accomplished for them in the matter on which I am writing. Such patients more properly belong to the realm of psychiatry.

The very large group of patients in whom I am particularly interested is usually seen by the doctor either in obstetric or family practice. This group consists of young married women, healthy both mentally and physically, who have given birth

to one or more children. These women are adapted to their environment, reasonably satisfied with their lives, and in love with their husbands. Much can be done for them. The sad part of it is that as a rule these patients would never think of asking their doctor for help and advice about sex matters. That is an integral part of the code that has caused most of the difficulties in their physical marital relations. The doctor must be alive to the need of a few sympathetic and tactful questions on the sex life of his patient, or the story will go untold. I will elaborate a typical case history, usually obtained at six weeks postpartum. One can easily read between its lines, the suffering in silence and tension that makes up the unsuspected background of what would otherwise be a happy home life. It goes as follows:

"Yes, my husband and I were very much in love when we were married. We still are."

"Yes, my first married sex experiences were quite painful."

"No, my husband was and is, quite considerate."

"Yes, after a while there was no pain, but I never seem to have any feeling."

"No, I never mentioned this to my husband."

"No, I didn't mind when I got pregnant, both my husband and I wanted children."

"Yes, we want more children, but not right now."

"No, we have not had intercourse since my baby was born. You see we were afraid and didn't know what to do."

"Oh, yes, if you will tell me something to do, I will be ever so grateful."

And then at the end of another six weeks or so: "Oh, doctor, I don't know how to thank you for what you have done for us. Why the way things are now, after that advice you gave me, there is all the difference in the world between my husband and myself. Why didn't someone tell me these things before I was married?"

What is this "advice" that has wrought such wonders in the family life of "Mr. and Mrs. Smith"? It is nothing either particularly new or very remarkable. It is a short and very simple lecture on sex anatomy and physiology. Such simple facts as the following are stated with clarity and dignity. That sex relations are and should be a matter of mutual concern, that the wife can and should experience as much spiritual and physical gratification as her husband, that by so doing she will add one hundred fold to the bond that exists between her-

self and her husband and the general happiness of her married life, that orgasm on her part can occur, and should with reasonable frequency be simultaneous with her husband's, that in order to achieve this result, complete frankness is necessary between wife and husband, and that as a prelude to sexual union, certain acts of physical intimacy and endearment are not to be avoided but to be encouraged and welcomed, that instinct can and should be given free rein prior to and during coitus, and that where true love exists, there can be no such thing as that much abused and misunderstood term "perversion" These facts, coupled with instruction in a safe and practical contraceptive method, make up the lecture

Since the Catholic Church has officially* given its sanction to the principle of birth control, and has recommended the utilization of a physiologic method based on the relationship of ovulation to menstruation to accomplish this purpose, there need be no hesitancy in mentioning the topic of voluntary family limitation to patients, regardless of their religious denomination

Dickinson has emphasized the advantage of premarital examination and advice, with which program I heartily concur, but this method of attacking the problem is of very limited practical application There is at present, no recognized method that can get a patient to consult the doctor for premarital advice Though it would be highly desirable to have the clergy refer prospective brides and grooms to the medical profession for premarital examination and advice, such a custom is not likely of immediate development

The great opportunity at present, since our educational system neglects the giving of any medical education in its curriculum, lies with the physician who sees maternity patients following delivery Any doctor who has seen a patient through pregnancy, labor, delivery and the puerperium, must have won her complete confidence At this time the stage is all set, the patient deeply grateful and in the mood for confidences

* "The Rhythm of Sterility and Fertility in Women," by Leo J Latz
M D, Chicago, Latz Foundation, Chicago, Publishers

of an intimate and personal nature. The doctor should be definitely conscious of this favorable moment and take the initiative. The utilization of this opportunity gives the medical profession a chance to achieve one of our loftiest ideals, the elimination of needless human suffering.

CLINIC OF DRS RUSSELL RICHARDSON AND MORRIS A BOWIE

METABOLIC CLINIC OF THE HOSPITAL OF THE UNIVERSITY OF
PENNSYLVANIA

SOME PRACTICAL CONSIDERATIONS IN THE MANAGE- MENT OF JUVENILE DIABETES

Introduction.—Juvenile diabetes differs in several important respects from the disease as seen in adults. Usually it may be regarded as a "primary" disorder of metabolism, uncommonly preceded by obesity or degenerative changes which often foreshadows the onset of diabetes in adults. Of our cases not one was overweight at the time of onset. Heredity probably accounts for the majority of juvenile cases.¹ Two patients of our group are sisters whose diabetes appeared at the ages of seventeen and nineteen respectively.

In the adult the basal metabolic requirement remains more or less stationary from year to year, at least in the normal and probably in the diabetic as well. Children, on the other hand, have a shifting requirement, which any type of dietary treatment must anticipate. The extra caloric intake necessary for growth and activity must be considered. For practical purposes, that lost as the result of the specific dynamic action of protein and that unutilized may be disregarded except in the very young, or in failure of growth. The amounts of protein must be sufficient for maintenance and growth, and it is, of course necessary that some of this protein should be of the 'first class' variety in order to include the 'essential' amino acids. The growing child needs at least 1 Gm. of calcium per day. Smaller amounts of iron and iodine are requisite.

Another fundamental difference between the adolescent and adult diabetic is the lack on the part of the former of a clear conception as to the necessity for strict dietary regulation. The child diabetic meets gustatory temptation at home, at school, and at play at a time when he is not temperamentally able to withstand it.

The frequency of coma is so high in juvenile diabetes that Joslin³ has said, "It is characteristic of the disease in children." Half of our cases have had coma once or oftener. Dietary lapses account for the majority of these, but a sizable number occurred because the patient "had run out of insulin," had failed to take any, or had taken an insufficient amount.

MAINTENANCE OF THE NORMAL NUTRITION

Diet—The introduction of insulin has not lessened the need for a workable understanding of the simple dietetic fundamentals. The most practical methods are the use of simple diet lists which may be made up by the physician or a dietitian. Both children and parents should learn the common starchy foods. We have insisted that our patients learn the members of the 15 to 20 per cent groups, the remainder can be lumped together. Their use of cereals and cereal products is specifically limited. Usually cereal is allowed at breakfast, cooked cereals are easiest to measure and somewhat more bulky. For these reasons they are to be preferred to the dry. It is a common misunderstanding that whole wheat, gluten, or other dark breads may be eaten with impunity, the high protein content of many of these products, over 50 per cent of which may be utilized as glucose by the organism, may throw the dietary adjustment out of balance. Furthermore, many contain little less carbohydrate than white bread and are distinctly less palatable.

Relatively high carbohydrate ratios in the diet increase the palatability, a feature which cannot be overlooked. The average carbohydrate employed in children prior to 1925 in this clinic was 83 Gm, in the same group of patients the average carbohydrate in 1935 is 165 Gm. The deleterious effect

of a low carbohydrate, moderately high fat diet is illustrated by the following case.

Case I.—A white boy developed weakness and loss of weight in 1922 at the age of twelve. This followed an attack of scarlet fever. He was hospitalized in 1923 the positive physical findings were emaciation and carious teeth. Blood sugar was 314 mg. The urine showed glycosuria and ketonuria. The latter persisted and was present at the time of discharge he was sent home on a diet of 53 Gm. protein 125 Gm. fat and 60 Gm. carbohydrate. The insulin dosage was 15 units before breakfast 10 before lunch and 15 before dinner. Height was 148 cm. (58 inches) weight 68½ pounds. The patient reported irregularly to his physician and once to the clinic in 1931 at which time he weighed 131 pounds. He was then taking 20 units of insulin twice daily. Examination in April 1934 when he next reported to us, revealed poor posture carious teeth bilateral cataracts and evidence of an insufficient arterial circulation in his feet. Weight had increased to 136 pounds. Height was 160 cm. (63½ inches). Blood sugar was 160 mg., and plasma cholesterol 500 mg. Insulin dosage had remained the same throughout the previous three year period.

Comment—Though this patient has escaped acidosis and coma, the continued use of a relatively high fat diet with some glycosuria at times probably aided in producing two serious complications, cataracts and arteriosclerosis of the peripheral arteries.

Geyelin's experience with the inhibiting effect of high fat diets⁴ on the carbohydrate tolerance, and our impression that wounds heal more rapidly on high starch allowances have convinced us of the desirability of as near a normal carbohydrate fat ratio as is possible. The above patient was content with his diet and did not desire a change needless to say his preference did not deter us from altering it.

In the more reliable and intelligent patients we have resorted to substitutes as outlined by Rabinowitch² for bread, potatoes or other high carbohydrate articles. Jelly, ice cream, and nuts can thus be employed to some extent. Brazil, cashew, hazelnuts and walnuts are allowed to some, particularly those younger patients in whom a high protein and high caloric intake is essential.

The caloric value of the diet must be sufficient to promote fairly consistent gain in height and weight and these may be taken as evidence of a sufficient intake. We have not found

the determination of the basal metabolic rate essential in estimating the basal requirement, though in a few cases it has been desirable. Reference to the tables of Benedict or Aub and Du Bois will cover the average case. If regular gain in height and weight does not occur, the actual dietary intake should be carefully checked and altered if insufficient.

The protein requirements are higher for the juvenile diabetic than for the adult. The following table taken from White⁶ shows the protein and caloric minimums

Age	Cals/Kg	P/Kg	C	Average diet in grams			Cals
				P	F		
5	75	3.0	140	60	70		1400
10	65	2.5	160	70	80		1600
15	45	1.5	180	85	90		1900

Insufficiency in this regard over a period of time may result in pseudodwarfism of the diabetic type. Pseudodwarfism may occur in spite of high protein feedings as in one of our patients, a girl of twenty, whom we are forced to classify as such. Glandular dysfunction may partially account for these failures to attain adult weight and stature. Steady increase in height and weight is to be expected as in a girl of five who weighed 16 Kg (35 pounds). Her initial diet allowed 50 Gm of protein or 3.1 Gm per kilogram of body weight. At the age of nine, with weight of 25 Kg (55 pounds) she utilized 70 Gm of protein or 2.8 Gm per kilogram. A thirteen-year-old boy in our clinic weighing 39 Kg (86 pounds) requires 85 Gm of protein to insure constant gain in height and weight. Continuation of a relatively high protein intake may be desirable even through the late teens and early twenties.

An adequate intake of calcium, iron and iodine is particularly important in the juvenile diabetic. Part of the calcium requirement is supplied by milk, of which at least a pint a day should be taken. Hemoglobin estimation and red cell counts at intervals indicate the need or sufficiency of iron. It is our custom to add cod liver oil to the diet, making allowance in the fat intake, throughout the fall and winter. This is especially indicated in those children who appear thin without neces-

sarily being underweight, in those susceptible to upper respiratory infections, and in those cases showing caries of the teeth. Occasionally, in the latter, we have added calcium lactate.

Insulin.—The amount of insulin required will be governed by the severity of the diabetes, the character of the diet, and the extra quota needed to provide growth and development. The smallest amount used in any of our patients is 15 units, this is the morning dose for a girl of fifteen whose diabetes has been present for five years. The highest dosage is 92 units for a boy of eighteen who has passed his fifth diabetic birthday. A number of others receive as much as 60 or 75 units.

The total daily amount is usually divided into two or three doses. Rarely does one dose suffice. Some patients could easily be maintained without glycosuria with only one dose, but gain in weight and height would not occur so satisfactorily. The greatest number of units, usually about $\frac{1}{2}$ of the daily total, is administered in the morning, about a half hour before breakfast. These doses range, in our patients, from 15 to 59 units. The evening dose is uniformly smaller except in a few of the older patients who work and prefer their largest meal in the evening. A certain number need a much smaller dose at 10.30 or 11 P. M. One patient sets her alarm for 3 A. M. in order to take her insulin. She has become so accustomed to this routine that it never interferes with subsequent sleep. In this latter group, it is impossible to prevent considerable glycosuria in the early morning specimen except by the late night dose. Rarely are reactions encountered while the child is asleep and if the parent notes suspicious symptoms the dose can be lowered or a small amount of carbohydrate can be taken at the time insulin is given.

An interval of half an hour is the usual time between the injection of insulin and the beginning of the meal. If the 11 A. M. specimen shows sugar we sometimes add the lengthening of the interval to forty five minutes or an hour, as the food is digested more rapidly than the insulin. In a very few cases in which we have demonstrated a low afternoon blood sugar the patient takes his evening dose an hour after the evening meal.

Spacing of the meals is a practical point sometimes overlooked by the clinician in an attempt to find an explanation for glycosuria. Some patients, because of habit or expediency, eat the three meals within eight hours or less. If possible we urge our children to allow five hours between meals, hoping thus to stimulate their own insulinogenic function.

Scrupulous care in the sterilization of the syringe outfit is essential if furuncles and septic abscesses are to be avoided. We strongly urge each child to boil his own outfit (under supervision if he is under ten years of age) and never to rely on alcohol in which many patients keep their syringes and needles. Several years ago we found an instance of apparent precipitation of the protein fraction of insulin by alcohol. If the patient plans to travel and cannot conveniently boil his syringe and needle, we advise use of iso-propyl alcohol* instead of the usual grain alcohol.

Each child is repeatedly instructed in the necessity of injecting insulin according to an imaginary checker board design, using each limb and if necessary the back, with parental assistance. Lipodystrophy may result otherwise, and if insulin is injected into such an area, its absorption cannot be assured. In one adult we have seen a marked muscular atrophy of the deltoids, biceps, part of the quadriceps, and the glutei from repeated injections over a small area. With better spacing, massage, and exercise, the atrophy disappeared.

Regulation of Activity—Every juvenile diabetic and at least one parent or close relative should be taught to make the Benedict qualitative test for urinary sugar. In the more stable patients, such tests need be performed but once weekly on specimens passed at 7 and 11 A. M. and 4 and 9 P. M. In the less stabilized and in the younger, more active patients, routine daily testing of one or more specimens is advisable. The evening dose of insulin, *e. g.*, can be adjusted according to the urine test. One patient receives a dose varying from 8 to 15 units, depending on how active he has been in the early afternoon.

* Eli Lilly or any reliable drug house

Usually, these children play normally or indulge in hard physical exercise. No curtailment of activity should be allowed except during menstrual periods in the girls. Occasionally, extracurricular school duties have taken so much of the afternoon that little time is permitted for exercise. In such instances we have stressed the greater importance of the latter, setting up exercises and calisthenics are to be recommended for some.

PREVENTION OF COMPLICATIONS

Acidosis and coma are still the bugbears of the juvenile diabetic. Both the child and his parents must be on the alert at all times to guard against them. Proper understanding of the relationship of 'the three steeds, diet, insulin, and exercise, which pull the diabetic's chariot' ¹ will do much to reduce the incidence of these dreaded accidents. Any gross alteration in any one of them demands modification in the other two. The infections to which childhood is highly susceptible should always be under the watchful eye of the physician, simple colds come under this category as well as the exanthemata and more serious illnesses.

Dietary lapses, failure to take insulin or to take a sufficient amount also cause many cases of coma. Whenever a child feels ill and in addition has sugar and a positive ferric chloride test in the urine and an acetone odor on the breath, a diagnosis of acidosis may be made. At this time it may be possible to avoid coma by immediate: (a) Rest in bed, (b) fluids by mouth, especially hot and well salted, such as broth, (c) insulin in increased doses from 20 to 50 units repeated if necessary and (d) sugar by mouth such as orange juice containing sugar in order to have glucose in the body to balance the insulin. If one remembers that the juice of a medium sized orange and a heaping teaspoonful of sugar each contain 10 Gm. of sugar one can easily give them with insulin in the proportion of 1 to 2 Gm. of sugar to each unit of insulin. No harm can follow a large dose of insulin if there is sufficient sugar in the body to balance its action. The leukocyte count is usually

high in acidosis For this reason any operation should be deferred until further study makes clear whether this leukocytosis is due to an infection causing acidosis or to the acidosis itself In previous numbers of Medical Clinics of North America the treatment of coma has been dealt with authoritatively

Case II—We should like to mention an unusual cause of coma as recently seen in one of our patients, a young girl of nineteen, whose diabetes has been present for four years Her bowels became constipated, and a week passed without a defecation At the end of this time slight anorexia appeared late one afternoon She reduced her evening dose of insulin a little because her appetite was not up to par By 8 P M that evening vomiting set in, followed later by abdominal pain Three hours later she was comatose The family physician transferred her to a local hospital A leukocyte count of 50,000 suggested an associated inflammatory condition, but the surgical consultant wisely refused to intercede Nevertheless, a lumbar puncture was done With treatment of the acidosis, all symptoms disappeared within twenty-four hours, and the patient made an uninterrupted recovery

Comment—Coma supervened quickly in a young diabetic who had been well most of the day No infection of the nose, sinuses, throat or other organ could be located Several enemata produced voluminous masses of feces We surmised that vomiting had been initiated by the obstipation, and the loss of fluids precipitated the acidosis This patient's mother died several years ago and since then she has taken over most of the household duties She felt so guilty about her constipation that she was ashamed to tell her father

Two of our patients have well-marked, bilateral cataracts One of these (Case I) has never been hospitalized for acidosis or coma His present condition illustrates the result attendant on poor cooperation and the apparent harmfulness of a low carbohydrate, relatively high fat diet His is the only instance of well-marked arteriosclerosis though several patients exhibit retinal arteriosclerosis of a + or ++ degree The second case has been treated on three successive occasions for coma A few other cases show cloudiness of the media

In our opinion the estimation of cholesterol and total blood fat is important in the management of a diabetic The former

is actually sufficient since it reflects with more or less accuracy the level of blood fats⁹ The statement that absence of glycosuria is always attended by a normal cholesterol and blood fat does not accord with our experience. In 3 patients, 2 of whom are always sugar-free, the cholesterol figures have ranged from 385 to 500 mg per 100 cc. In the third only one of 4 specimens contains sugar The blood sugars range from 140 to 250 mg at the highest. We agree with White that moderate restriction of cholesterol rich foods (eggs, butter) is desirable¹⁰

Tuberculosis has been diagnosed in but 3 of our cases, and in all of these it is now arrested We think every diabetic, young or old, should have a physical examination and chest x ray at regular intervals¹¹

During the period of initial standardization, an experimental insulin reaction may be done on each patient in order to acquaint him with the aura and train of symptoms which he can expect whenever he inadvertently eats too little, exercises too hard, or takes too much insulin It has been our experience that the symptomatology of this condition follows a regular pattern in each individual with but little variation, though individuals may vary Some of the "classical" symptoms were never seen during active investigation of insulin reactions several years ago¹²

PSYCHOLOGICAL PROBLEMS

Home Attitude—Each juvenile diabetic should have a "big brother" or "big sister," preferably his father or mother, or both However, the supervision should never devolve entirely on one individual to such an extent that vacations away from the patient are impossible Each diabetic child should eat at the table with the family even though he must weigh his food on a scale or in household units Segregation at meal times may breed morbidness and a feeling that he is a pariah This injunction does not, of course, apply to the very young child Some of our families have materially altered their dietary habits since the advent of diabetes within

their family circle. Usually this has been for good, as in the substitution of fruits and plain desserts for pastry and rich puddings. This action removes considerable temptation from the child.

Some families unwittingly develop an attitude of discouragement which sooner or later reflects itself in the diabetic child. The mental reaction usually has its basis in the hearsay evidence and gossip of friends. Occasionally, a gradual increase in dosage of insulin may give rise to such a notion, careful explanation of the increasing metabolic needs for growth and activity which necessitate larger amounts of insulin will usually clear the atmosphere.

School—It has been our custom to write letters to the teacher directly most responsible for the child, often to the principal or superintendent as well. In these, chief attention is placed on the possibility that irregularities in behavior may be due to insulin reactions, a brief list of the common symptoms of hypoglycemia is appended. We hesitate to ask the teacher to "police" the child during recess periods when he may acquire candy or sweets from his playmates, but she is requested to intercede if such exchanges come to her attention.

Parents of diabetics should not allow the child spending money until he can be trusted implicitly. If possible we permit a small orange or apple at one recess period. This suffices ordinarily to satisfy any craving for food and makes the child content with his lot.

Unless good reasons exist, no excuses are given to permit escape from gymnasium or playground drill, which the diabetic as well as the normal child may dislike. Such reasons rarely arise. On the other hand, the importance of exercise is stressed to both the child and his parents.¹³

A few of our patients, especially the girls, manifest a desire that knowledge of their disease be kept from playmates. We see no harm in this even though a sense of shame may underlie the attitude, and we often recommend that she take close friends into her confidence. We have found among pa-

tients that usually only a few intimate friends are familiar with their condition

Personal Training—Every diabetic should learn simple diabetic arithmetic, and ought to know the more common foods which are permissible and those which are forbidden. Familiarity with the 5, 10, 15 and 20 per cent vegetable lists is not absolutely essential, but once the child's interest is aroused, he will quickly learn these of his own accord. The use of scales for accurate measurement is again not requisite, a few of our patients, however, talk in terms of grams rather than in household measures. One boy, aged ten, weighs his food and administers his own insulin.

A good manual has often stimulated the child's interest to learn more about his disease and its control. Some of the children have shown eagerness in earning enough money to purchase one.

To encourage self reliance and stimulate the pride of the juvenile diabetic should be the task of physician and parents. The refractory child and even the "contra repeater" can often be made the most cooperative patients once the seed of pride has taken root. Minor setbacks and occasional glycosuria should never occasion a reprimand or scolding. On the other hand a sympathetic understanding and encouragement will often work wonders with the recalcitrant child.

The experience gained in summer camp for diabetics is often valuable to the child. Some of our patients have been able to care for themselves adequately in camps where no dietitian is at hand. Usually the insulin dosage can be reduced because of the greatly increased activity.

ILLUSTRATIVE CASES

POOR RESULTS

Case I (adult)

Case III. A mulatto girl of seventeen was first seen in March 1931, complaining of weakness, polydipsia, polyuria and loss of weight. Examination showed glycosuria, ketonuria, xanthopsia, anemia and a few vulvar funicles. Treatment was operative. The local physician later sent her to another hospital for treatment of accident. On three subsequent admissions there can be seen (Fig. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100). In 1932 she was referred to the University Hospital for

coma The CO_2 combining power was 5 volumes per cent, the blood sugar 400 mg Recovery was prompt with 280 units of insulin and fluids On this occasion the blood Wassermann was strongly positive She was referred to the metabolic section Her diet contained 100 Gm of carbohydrate with 65 units of insulin Admitted dietary indiscretions and frequent omission of insulin resulted in acidosis in 1933, at which time 440 units of insulin were necessary to produce improvement In March, 1934, she complained of amenorrhea and morning nausea, the uterus was the size of a three months' pregnancy A therapeutic abortion and sterilization were performed At the present time her diet consists of 70 Gm of protein, 80 Gm of fat and 200 Gm of carbohydrate with 70 units of insulin in two doses Glycosuria in one or two specimens persists and the average blood sugar is 200 mg Weight is 142 pounds Antilutetic treatment has been carried on as regularly as the patient will allow

Comment—Heredity is probably the etiologic factor in this case, the maternal grandmother died of diabetes and a sister has recently developed it at the age of nineteen The patient's main difficulty is lack of intelligence though the moral laxity is a contributing factor Her sister is apparently resolved to tackle the situation more intelligently

GOOD RESULTS

Case IV—A white boy of thirteen developed diabetes in 1921 In 1923, 1924, 1925 and 1927 he was hospitalized for coma He reported to the metabolic section in the latter year at which time his diet consisted of 80 Gm of protein, 150 Gm of fat, and 100 Gm of carbohydrate with 60 units of insulin In 1931, he noted abdominal pain while eating dinner He was sent to the surgical service by his local physician, the patient said that he was a diabetic Operation was deferred until laboratory examination showed a mild acidosis and a normal leukocyte count He has remained well since then and on his fourteenth diabetic birthday he weighed 150 pounds (height 68½ inches) His diet for the last three years has consisted of 70 Gm of protein, 77 Gm of fat and 170 Gm of carbohydrate, with 63 units of insulin The blood sugars vary from 70 to 212 mg, urine specimens are regularly "sugar-free" There is no roentgen evidence of tuberculosis or peripheral arteriosclerosis

Comment—The above patient is well along in his second decade of diabetes In spite of acidosis and coma on five occasions, the only complication is slight haziness of the media It is interesting to note that the diabetes has not increased in severity, the insulin requirement is slightly less than in 1924

Case V—A white boy developed diabetes in 1925, at the age of seven-teen Coma supervened four times within the next two years In 1931, an

upper respiratory infection precipitated mild acidosis. Right apical tuberculosis had been diagnosed by x ray in 1927 four years later a quiescent lesion in the left apex was noted. A diet of 70 Gm of protein 100 Gm of fat and 200 Gm of carbohydrate with 115 units of insulin daily was necessary several years ago. With improvement the insulin dose has been reduced to 75 units daily. The blood sugars average about 200 mg while the urine usually remains free of glucose. Height and weight are within normal limits.

Comment—The presence of inactive tuberculosis makes us hesitate to reduce the heavy insulin dosage lest a flareup occur. At the time of writing his health is excellent, and no other complications are in evidence.

All the above cases with the possible exception of Case I are examples of severe diabetes whose early diabetic lives were stormy. Periodic attendance for treatment and education, and probable stabilization of their metabolism with the attainment of their majorities has brought about improvement.

SUMMARY

- 1 The chief differences between juvenile and adult diabetes have been briefly discussed.
- 2 Some of the practical features of dietary management and insulin administration are presented.
- 3 The more common psychological problems as seen in this clinic are reviewed.
- 4 Several cases illustrating poor and good results, have been briefly outlined.

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CLINIC OF DR AIMS C McGUINNESS

CHILDREN'S HOSPITAL

THE TREATMENT OF ENURESIS IN CHILDHOOD

THERE is no behavior disorder which has called forth so much literature as urinary incontinence in children and the articles on the subject serve to indicate by their large number alone how far we are from a final solution to the problem. The theories for its causation run from the sublime to the ridiculous. One writer has stated seriously that he believes that all boy enuretics have a suppressed desire to become firemen. Others have attributed the condition to diseased tonsils. The methods offered for the treatment of enuresis are legion, and investigators have suggested everything from caviar to epidural injections of saline.

Pediatricists and psychiatrists are coming more and more to believe that enuresis is purely a functional or psychic disturbance and it may be defined, as it will be considered in this paper, as functional incontinence of urine, either nocturnal, diurnal, or both, in children of three years of age or over. It is felt by most investigators that children are usually able to develop bladder control through proper habit training by this time.

Statistics on the incidence of enuresis are not very reliable. It is said to occur in about 12 to 15 per cent of all "nervous" children. This grouping is obviously vague and indicates that real statistical data are lacking. Boys and girls are equally affected regardless of race and social status. An analysis of

hereditary factors reveals that bed-wetting was a childhood problem in one or both parents in from 30 to 40 per cent of cases of enuresis studied by several different authors. Frary has recently studied the pedigrees of 59 clans in which there have occurred one or more enuretic children and as a result of her findings proposes the hypothesis that enuresis is an hereditary trait determined by a single recessive gene substitution. With our present knowledge it would seem to be a fallacy to attribute an hereditary factor to enuresis other than to say that children are apt to be more or less the emotional prototype of one or the other of their parents.

The various theories for the causation of enuresis may be divided into three groups. Physical, neurogenic, and psychogenic, the neurogenic factors really being a subdivision of the physical factors. According to the definition of enuresis here adopted the types encompassed in the first two subdivisions are really not simple enuresis at all, but rather are to be considered as cases of urinary incontinence which may simulate enuresis.

Physical causes of enuresis

- 1 Constitutional disorders such as diabetes insipidus, and mellitus
- 2 Renal infection
 - (a) Nephritis
 - (b) Pyelonephritis
 - (c) Pyonephrosis
 - (d) Hydronephrosis
 - (e) Tuberculosis, etc
- 3 Renal, ureteral, or vesical calculus
- 4 Cystitis
- 5 Urethritis
- 6 Trigonitis
- 7 Congenital malformations
 - (a) Urethral or vesical neck obstruction due to stricture, hypertrophied verumontanum, congenital posterior urethral valves, etc
 - (b) Hypospadias

Neurogenic causes of enuresis

- 1 Sympathetic parasympathetic imbalance and vago-tonia
- 2 Spina bifida occulta
- 3 Cord bladder resulting from other pathology of the central nervous system

Psychogenic Causes of Enuresis—The psychogenic conception of enuresis maintains that this phenomenon is an external manifestation of mental conflict of one type or another. Though not always the case, enuresis is but often one of a number of difficulties presented by the same patient, difficulties such as temper tantrums, anorexia, extreme negativism, and the like. Enuresis may be an aggressive act or perhaps more often a submissive one. Sometimes enuresis is an aggressive act in a very submissive child. It may arise from such strong emotions as fear, hatred, jealousy, and inferiority. A child is at once at a disadvantage in the presence of adults in that he is physically unable to meet them on an equal ground. No matter what the adult may do, however, the child is the sole master of his function of elimination, and he can always employ this route for voicing his protests.

The process of growth requires a child not only to take on added responsibilities but also requires that he give up as he matures certain of the more pleasureable things of his early life, for instance, having his diapers changed and voiding whenever he likes. When certain things in connection with his growing up become unbearable, it is all too easy for him to regress to or retain those things which he enjoyed in infancy.

In addition to the factors of growth it must be remembered that there is nothing that a child enjoys more than attention, and bed wetting is one method through which this end is almost sure to be attained. Often it will be found that a child has developed his enuresis following a severe illness during which time he received considerable attention from his parents. When he has recovered from his illness he immediately ceases to receive the close attention which was showered upon him.

while ill, and here the enuresis is an attempt on the part of the child to regain some of the favor lost by getting well

A brief consideration of the essentials in 3 cases of enuresis chosen at random may help to illustrate some of the points mentioned above

Case I—Joseph, aged nine, a most aggressive child, was very fond of his father. When he was about four years old his father and mother were separated. All went well so long as Joe's father visited him at frequent intervals. Several months before Joe was referred to the clinic his father ceased to pay the usual visits and Joe immediately developed intractable enuresis, nocturnal as well as diurnal. It is interesting that during the period that Joe was wetting himself day and night at home he paid a brief visit to the home of his paternal grandparents where his father was staying. The enuresis stopped immediately only to return as quickly when the visit terminated. At school Joseph was a model of propriety.

Case II.—Grace was a very shy and sensitive girl of ten. She had two rather aggressive younger brothers who were unquestionably the family favorites. Grace was very much overprotected and was not encouraged to help herself in any way. She did good work at school, but did not have many playmates. Grace had wet the bed since the age of four in spite of every effort on the part of her parents to cure her. When she was stimulated to take on a little of her own responsibility and develop some interest in life her enuresis promptly stopped.

Case III—Gabriel, a rather effeminate and pretty boy of seven, was placed in the home of his paternal aunt when his mother developed tuberculosis and had to be put in a sanatorium. He was thrown in with five robust and aggressive cousins and the situation was too much for him to handle. Enuresis developed promptly and continued nightly in spite of all the routine measures which his aunt could produce.

In spite of the growing feeling that the majority of cases of enuresis are purely functional in origin there are a number of so-called "symptomatic therapeutic procedures" which have been employed for many years and which still form a major part of the armamentarium of many authors who write on the subject. Before discussing the psychiatric management of enuresis a few of these procedures will be considered because of the fact that they have been so universally employed.

1 Restriction of fluids

Discounting the fact that if a large amount of fluid be taken before bedtime it will be necessary to empty the bladder before morning, there is little scientific evidence to support this pro-

cedure There is no evidence to show that the bladder capacity of enuretics is any less than that of the nonenuretic child Many an enuretic will have a series of dry nights when on a normal fluid intake and then wet the bed every night for weeks upon end when fluids are markedly restricted

2 Awakening at certain intervals during the night to empty the bladder

This is likewise an almost routine procedure The same thing occurs here as when fluids are restricted It seems a remarkable thing, but in a persistent enuretic no matter how many times he is gotten up to void he will invariably find enough urine to wet the bed if he so desires

3 Atropine and other drugs

Atropine in some form or other has been a standard drug for many years, and in spite of the fact that its action on the bladder has not been conclusively determined, a number of the best investigators feel that it may exert some beneficial antispasmodic action It is more probable that suggestion plays a large part in the positive therapeutic effect of this and any other drug that may be employed

4 Star charts and rewards

Provided the case is progressing satisfactorily star charts may encourage a child and undoubtedly have helped in many cases The same applies to other rewards For the most part, however these measures only tend to concentrate the child's mind on the magnitude of his problem and when the case is not progressing satisfactorily they only discourage and humiliate

5 Elevation of the foot of the bed, avoidance of sleeping on the back, exercising the sphincter, epidural injections of saline, stretching the bladder by hydrostatic pressure, and so forth have all been advocated at one time or another and these methods as well as those mentioned above have often succeeded The mechanism of the success which they may have attained is probably one of suggestion Zepfert (quoted by Anderson) summed up the therapeutic endeavors against enuresis as being either symptomatic or suggestive In the first

group he places restriction of fluids, awakening at stated intervals, restriction of diet, and general upbuilding of the body. All other methods are suggestion therapy even "including atropine." I should be inclined not to make the above division and to place all methods for the correction of enuresis under the heading of suggestion. Physical measures have probably been successful when employed by a person capable of instilling sufficient confidence in the patient to enable him to overcome his own affliction.

In undertaking to treat a case of enuresis from the functional standpoint it is well to remember that there are a certain few cases of urinary incontinence which are based on an organic disorder. A thorough physical examination and repeated urinalyses are indicated in every case, but at the start it is advisable to conduct one's examination in such a way as to direct as little manifest attention as possible on the genito-urinary tract. It is also advisable not to discuss the child's problem in his presence because this, as do urological examinations, only fix the problem more firmly in the child's mind, and increase its magnitude to such a degree as to make it all the harder for the child to overcome his trouble. It is important to investigate the emotional surroundings of the patient and to help the parents to a better understanding, for as long as the parents are obviously worried and distressed the child will be hindered in his progress.

Most children are extremely sensitive about their enuresis and prefer not to discuss it. Therapy should be directed toward helping the patient to a better understanding of himself and toward instilling in him a spontaneous desire to grow up and overcome his difficulties. The statement that a child will stop wetting his bed when he wants to and not before, is a very apt one. It is this desire on the part of the child to meet the situation himself which is the end which should be striven for. This may be accomplished through conversational interviews with the child, interviews conducted by a person who, with the assistance of toys and other playthings, will allow the child to be free to introduce into the conversation anything about

which he may wish to talk, which might include enuresis. It is often nothing more than the understanding friendship which may develop between the therapist and the patient which will give the latter the self confidence which he needs. Many of these children have never had the experience of discussing their lives with an absolutely impartial and understanding adult. Relatives and the school teacher are associated with a part of the child's life which is characterized by restrictions and discipline representing the very things to which he has not been able to adjust himself. The therapist who lies completely outside the realm of family and school is in a position to bring out and mold the plastic and immature thoughts of the child in such a way as to give him confidence in himself which he can get in no other way.

No set rules can be laid down for carrying on psychiatric interviews with enuretic children, for no two cases are exactly alike. It is necessary to keep certain principles in mind and to follow these principles through whatever medium the individual case may offer. These principles in general are: Making friends with the child, gaining the child's confidence and interest, and allowing him more chance to develop new channels of activity and self-expression. Also, endeavoring to clarify parental attitudes toward the child, not only regarding enuresis itself but regarding attitudes and management of the child's entire personality. The reeducation of parents is important and usually difficult. There are times when this can be aided by having the parents read good books on child psychology and hygiene such as Cameron's 'The Nervous Child' (Oxford University Medical Publications), 'Big Problems on Little Shoulders' by Carl and Mildred Renz (The Macmillan Company), and many others.

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CLINIC OF DR J CALVIN HARTMAN

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PRENATAL SUGGESTIONS TO PREVENT KIDNEY DISORDERS

THE term "kidney of pregnancy" implies that the organ is in some way different from that found in the nonpregnant state. This is entirely fallacious, we are dealing with the same organ, subject to the same diseases as at any other time, it is only the overburdening of the normal kidney function in pregnancy with the subsequent disorders that gives rise to the term "kidney of pregnancy." When we realize that in each pregnancy we may be dealing with a kidney of low functional ability or one in which there exists a quiescent lesion from some previous exanthemata which may undergo an exacerbation, I wish to emphasize the desirability of protecting the kidney by more exacting and careful prenatal supervision. We all know the rules governing the prenatal care but we do not insist on vigorous and painstaking enforcement. It is only reasonable to expect an organ to perform normally over a longer period of time if it is not constantly taxed to the limit of its ability. It is true that the incidence of true or fulminating eclampsia is not demonstrably affected by prenatal care but it is just as certainly true that the frequent disorders of the kidney that are the result of overeating, overwork, loss of sleep, fatigue, exposure and bad habits are definitely lowered, and who can say that the improved general condition does not lessen the possibility of true eclampsia. Therefore I feel that we should increase our watchfulness and insist that our rules be followed minutely modifying them to meet each individual case. There are no set rules applicable to everyone, they must

be individualized and changed possibly on each succeeding visit, according to the patient's weight, general condition, blood pressure and urinalysis

We divide the pregnancy into three trimesters. Observing the patient in the first trimester, we find with the advent of pregnancy the patient is more or less demoralized, not only physically but mentally. She finds herself very easily fatigued, with no endurance, impatient, irritable and very emotional for no good reason, unable to remain awake, and mentally incapacitated to carry on in her usual manner. Coincident with this mental and physical breakdown come the physiological nausea and gastric irritability. All these physiological disorders can be very easily overcome and the patient made happy and contented by a plain understandable explanation of the cause, such as "Up to the time of pregnancy the patient is an energy producing individual with her metabolic processes producing energy, but with the advent of pregnancy she changes into a reproductive individual with coincident alteration in the metabolism. During this change which is completed in three months there is a decided loss of energy and endurance." This explanation makes the rules governing her behavior intelligent and practical rather than dictatorial. Rest during this period is most important, both mentally and physically—ten hours' sleep at night and frequent short periods during the day, so as not to tax her endurance. The diet should be bland and easily assimilable, high in carbohydrates and taken every two hours in small amounts. Sunlight, fresh air and light exercise in proportion to the patient's ability. The kidney must be kept active with a fair amount of water in small amounts. Regularity of the bowels must be maintained. Fatigue is the most prominent disorder in this period. Excessive fatigue can be controlled by intravenous glucose. Careful physical regulation and cheerful, optimistic but firm mental guidance through this stage will prevent too great a loss in weight, as well as the possibility of an acidosis with its attending disorders and the patient will be in good general condition to enter upon her second trimester.

This is usually the most normal and uneventful of the three stages, from the patient's viewpoint, for the gastric symptoms disappear, she feels astonishingly well and full of energy, and yet it is the most dangerous. It is during this period that harmful dietetic indiscretions are practiced, and excessive activities are indulged in which reflect to our disadvantage in the last trimester. We must be exceedingly on the alert and all our influence and teaching must be directed toward keeping the patient within normal moderate limits relative to her gain in weight, exercise, rest and diet. The diet should consist of three small to moderate meals daily, at regular intervals (regularity and size are of marked importance), with fruits and milk if hungry between meals. The bulk of the diet should consist of green vegetables, fruits and milk, carbohydrates to be regulated by the patient's weight chart and her needful activity. Fats can practically be eliminated. Protein in the form of meats in moderate amounts. Salt to be used sparingly. Some form of calcium should supplement the diet. During this period moderation in work and play is most important. Rest periods and proper diet should be constantly urged so as not to tax or strain the functional ability of any organ—not only the kidney—remembering that indiscretions in work or play, loss of sleep and overeating create products of fatigue that are just as poisonous and produce the same disorders as a toxemia, and that the patient's general resistance is lowered to such an extent that she is particularly susceptible to any infection such as colds, influenza, etc., thus adding a further strain on the kidney.

The weight chart and the general appearance of the patient are important points of observation in this period. Twenty to 25 pounds is the normal weight gain in pregnancy. The chart should not show more than 5 pounds a month in this period. A greater gain means a slight restriction in diet or a slight increase in exercise, depending on where the patient is at fault.

In the last trimester our watchfulness should be increased. It is during this period that most of the serious disorders manifest themselves, are of major importance and demand most

careful supervision Weight, blood pressure and urinalysis are of the utmost significance, and headache, substernal pain, edema and dimness of vision are the cardinal symptoms of approaching trouble A sharp gain in weight in this period is a premonitory sign often before any of the other symptoms appear The diet should be the minimum for the individual's needs, fats are eliminated, meats in small amounts consisting of lamb, chicken or fish, and these entirely eliminated in the last month Skimmed milk and green vegetables may be increased Exercise and work should be sharply reduced, exposure and fatigue must be guarded against Common colds should be treated as a major disease, with absolute rest in bed, light diet and free elimination of the bowels and kidneys The reserve power of the kidneys should be maintained during this period by more rest, careful elimination and dieting

Visits in this period should be every two weeks at least, and if there is any evidence of failing function they should be increased as often as necessary Good function of the kidney is maintained by good functional ability of the other organs Keep the patient's general condition in mind A sharp gain in weight, scanty urine, a ten-point rise in blood pressure, albumin, casts, headache, and edema, etc—any one or several of these symptoms calls for a pure milk diet, more rest, and magnesium sulphate daily If the symptoms do not improve in a reasonable time the patient should be hospitalized, put at complete rest on a milk and water diet, with daily blood pressure, urinalysis and a record of the intake and output If the symptoms under the above treatment do not improve or remain the same, it is better and safer to empty the uterus The induction of labor should be by the simplest method possible in each individual case Eliminative measures should be continued up to and after delivery The patient can be supported in labor by intravenous glucose, 200 cc of a 25 per cent solution every four to six hours if necessary Glucose at this time not only provides energy for the delivery but is a good prophylactic measure to guard against convulsions that are produced by fatigue from long labor and an acidosis that is the result of

the patient being unable to retain anything in the stomach. During labor it is very important to keep the patient free from emotional brain pressure and mental worry and to relieve and soothe. The blood pressure and even heart action should be estimated before and after any treatment is given. There is no need to hurry the delivery by cocaine or ether etc. It is good judgment to avoid as far as possible any operative interference. If the blood pressure is rising rapidly and convulsions seem imminent, 10 cc. of a 10 per cent solution of magnesium sulphate intravenously will give you still more time. While in labor and if there is any symptom suggestive of impending convulsions after delivery, these patients should receive our constant supervision until they are safely through the crisis. The question of the child's viability and chances in the ordinary run of cases should always be limited to the mother's safety. There is no one symptom or group of symptoms that will tell you when to induce labor. Headache and substernal pain with vomiting are two signs that command great respect. The use of hot packs in cases with a blood pressure of 150 by 100 or more often causes the patient to fall in labor thus solving the question of the method of induction. If the preceding care and watchfulness are given it will unquestionably lower the frequency of kidney disorders.

In the outline I am dealing with a case where the laboratory findings are normal and there are no intercurrent disorders.

CLINIC OF DR JOHN McK MITCHELL

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THE TREATMENT OF DIARRHEA IN INFANTS AND CHILDREN BY A DIET OF RAW APPLES

THAT there has been a marked decrease in both the incidence and severity of the diarrheas of infancy and childhood can be attested without benefit of statistics by all practicing physicians whose experience goes back a decade or more. Stricter regulation of milk and water supplies at their source and a more general understanding of their proper handling in the home, the widespread use of evaporated milk in infant feeding, more adequate refrigeration, better screening, have all contributed to a reduction in gastro-intestinal infections by the colon-paratyphoid-dysentery group of bacilli. A better grasp of the fundamental nutritional requirements of infants by physicians and a wider dissemination of this knowledge through well baby clinics, visiting nurses, and governmental pamphlets has resulted in a generally better state of nutrition among infants. The effects of diarrhea, especially those secondary to parenteral infection, are correspondingly less serious. In severe cases showing toxic symptoms and acidosis, the well staffed hospital is able more intelligently to apply specific therapeutic procedures designed to correct the chemical changes in the body brought about by the diarrhea with a corresponding reduction in mortality.

In spite of all these improvements diarrhea remains a constant threat to the infant and small child and is one of the commonest conditions to be met by the physician practicing among children. Latter day treatment in line with good

medical practice has resolved into a fairly well-established pattern. A period of starvation or semistarvation, during which barley or other gruels are given along with adequate water, may or may not be accompanied by a purge and enemas. Milk usually skimmed and boiled, with or without the addition of casein, or acidified milk or protein milk in some form is then given in gradually increasing amounts, along with other bland foods. Bismuth or bismuth and chalk mixtures, frequently paregoric, are added by most practicing physicians. In the majority of cases such therapy is efficacious. There remain, however, a considerable number who in spite of vigorous and early application of the principles outlined develop a protracted diarrhea, the troublesomeness of which needs no elaboration. For these any truly effective mode of therapy will prove a welcome aid to the physician. Such is the apple diet.

THE APPLE DIET

Since a description of the use of raw apples in the treatment of diarrhea in children by Moro¹ in 1929, a number of articles have appeared in the German literature witnessing its value and safety. It has been used with good results in a number of pediatric clinics in this country and Birnberg² has recently published a summary of the results of his experience, which was also highly favorable.

A course of treatment consists of the following. Thoroughly ripe, mealy eating apples are pared, cored and grated to a fine pulp. Paring may be omitted. All other food having been withdrawn, the child is offered from 1 to 4 tablespoons of this pulp each hour during the day. If an insufficient amount of apple pulp is consumed to meet fluid requirements, as will usually be the case, the diet is supplemented by liquids. Infants may be offered water in small amounts at short intervals, either along with or between the apple feedings. It is sometimes helpful to sweeten the water with saccharine. In the case of children, weak tea made with lemon and sugar may be substituted for water. It is permissible to sweeten the apple pulp with a small amount of sugar if it is refused because

of sourness, or some thoroughly ripe, mashed banana may be incorporated with it. The great majority of patients take the apple pulp well.

The amount of apple taken varies greatly with the age and nature of the patient. As few as 8 or 10 tablespoons are eaten in a day by some patients while others will take as many as 50, which is equivalent to about 20 ordinary apples. Better results seem to ensue in those cases in which larger amounts of apple are consumed. It is best not to fix an absolute limit for continuation of the treatment. In some of the milder cases twelve hours is ample. From twenty four to thirty six hours is sufficient in the majority of instances, while even seventy two hours may be necessary in the more severe cases or those in whom diarrhea has been of long standing. The time for terminating the diet must be judged individually on the basis of general symptoms and character of the stools. When formed or semiformal stools have appeared it is usually safe to terminate the diet within the next twelve hours. The time of appearance of such stools naturally varies greatly, but in general they may be expected within twenty four hours from the time treatment is instituted.

TRANSITIONAL DIET

At the termination of the period during which grated apple alone is fed, the patient is offered a greatly restricted diet for several days. No arbitrary period can be set for continuing this, but from two to three days generally suffices. Its constitution will be altered to suit the age of the patient. Two satisfactory transitional diets are suggested on page 304.

The nature of the stools and the patient's desire for food will largely determine how long this regime will be continued, as well as the rapidity with which a normal diet may be resumed. Skimmed milk, whole milk junket, baked potato, custard, jam, marmalade and cream cheese may next be added. The cream may then gradually be returned to the milk and meat, vegetables and fruits allowed in increasing amounts.

Best results are obtained if treatment is commenced shortly

	<i>Infants</i>	<i>Children</i>
Breakfast	Cooked cereal (no milk) Apple pulp (4 tablespoonfuls)	Cereal (with skim milk sufficient to make edible) Toast Cocoa (made with water)
Mid A M	Apple pulp (1-4 tablespoonfuls)	Apple pulp Cracker (saltine or soda cracker)
Lunch	Clear broth or bouillon Rice Junket (made from skimmed milk)	Broth or bouillon Rice Scraped beef or chicken Toast or cracker Junket (from seim milk)
Mid P M	Gelatin	Gelatin and cracker
Supper	Cooked cereal Apple pulp	Cooked cereal Toast Cocoa Apple pulp or banana

after the onset of diarrhea, but diarrheas of even long standing sometimes react favorably. A case was seen recently, who for six months had been having from 4 to 6 loose, foul-smelling stools daily with much mucus and occasionally blood. This patient had failed to respond to all of the ordinary therapeutic agents given prolonged trial with rigid adherence. He regained normal semiformal stools after two days on an apple diet (which was taken poorly), two days on an apple-banana-toast mixture and four more on a transitional diet. Stool culture did not reveal the presence of any of the dysentery group of organisms. No other treatment was given at the time except transfusion for a secondary anemia of moderate degree.

In my own experience the diet has proved most efficacious in those cases of diarrhea which may be classed as parenteral, in those associated with nondysentery infections of the gastrointestinal tract and in food poisoning. Due admission is made of the difficulties in too rigid an etiological classification of cases and of the relative infrequency of cases of proved bacillary dysentery.

A number of theories have been advanced to explain the action of the apple pulp. Prominent among these is the purely mechanical factor of a pulpy, highly absorbent mass in the in-

testinal tract. The indigestible cellulose of this mass in combination with pectin,² a colloidal substance of high buffer value present in apples, forms a favorable medium for the absorption and removal of bacteria and toxins. Other suggestions relate to the tannin which is found in apples and attribute the benefit to the astringent properties of tannic acid. Malic acid had also been offered as the primary factor concerned. In support of this is its presence in other fruits from which somewhat similar beneficial results have been obtained.

Grated apple pulp is surprisingly well taken by children and well received by parents. It is far superior in both of these respects to starvation or semistarvation. While on the diet children previously in obvious discomfort and even pain usually become quiet and comfortable. It checks the diarrhea and tenesmus, mucus and blood disappear from the stools, it helps correct dehydration. It may be given with safety to infants, some as young as three months having been reported.

The raw apple diet is not a guaranteed cure all for every case of diarrhea in infancy and childhood, but it is superior to any other mode of therapy in general use today and its effect in a large proportion of cases is little short of dramatic.

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growth of man and animals but it must be admitted that mass growth studies do not evoke reliable deductions which can be applied to the process of growth of an individual

In spite of the complexity of the problem and in spite of the multiplicity of variables, there have been many notable attempts to express the process of growth by means of mathematical formulae and to plot curves illustrative of such formulae

Casual examination of such efforts might fail to interest the practicing pediatrician in their ultimate practical value which is not at first apparent. But if biomathematicians and biologists could with fair unanimity agree on a mathematical expression of the rate of growth, valuable deduction might be made as to the nature of the growth process. New methods for the promotion and support of optimum growth would suggest themselves and reliable predictions would be possible.

Increase in mass and increase in total length, or stature are the criteria customarily used to evaluate the process of growth. So universal has been this custom that one falls too readily into the error of considering these items as the process itself. One easily forgets that the growth of a child is the summation of the growth of a number of highly differentiated tissues, that weight is an objective measure of the mass of these tissues plus the fluids of the body, that height is a component of the skeleton modified by posture.

For use in comparison the conventional curve of the increase of weight during infancy and a typical curve of increase of weight during life are illustrated in Figs 23, 24. It should be remembered that these curves represent the mean values (or theoretical mean) of the weights of hundreds of infants and children. They do not represent the normal curve of growth of any individual child. Considerable variation is regularly observed in healthy children as has been pointed out by numerous observers.

Robertson² and Ostwald³ almost simultaneously announced that growth did not occur at a uniform velocity throughout life. They pointed out that there seemed to be three segments

INFANT'S WEIGHT-CHART

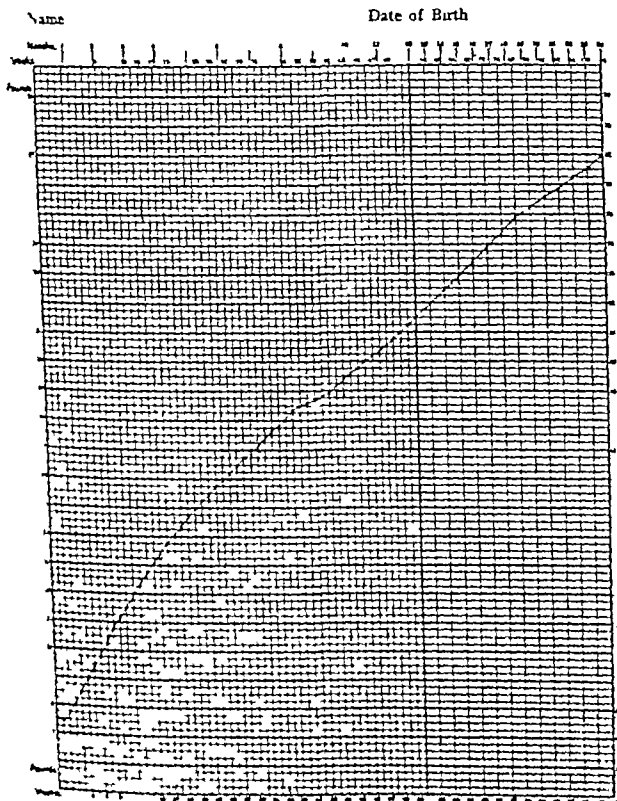


Fig. 3.—Conventional chart illustrating average weight curve of infants from birth to two years (Growth and Mutchell "Diseases of Infants and Children").

or cycles of growth which together comprised growth (Fig. 25). To explain the significance of these cycles Robertson

pointed out the similarity between the mathematical expressions of the graphs of these cycles and those of certain reactions known as autocatalytic, and deduced that growth was an autocatalytic reaction taking place in the body. He felt that certain products of the process of life itself, already proceeding at a uniform velocity, acted as catalysts and accelerated the process. To explain the retardation of growth in the latter part of each cycle, Robertson postulated the formation of growth inhibitory substances. This phase of his theory at

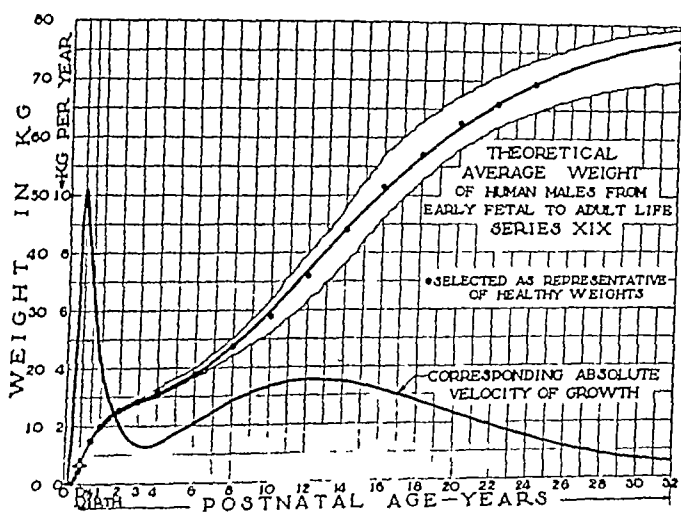


Fig 24—Conventional curves of progress of mean weight and velocity of growth, really velocity of gain (Wetzel in Proc Soc Exper Biol and Med, 1932)

least has been supported by actual demonstration by Carrel and others

This theory has been the focus of considerable discussion among biologists and while it has not been universally accepted, it still is the most prominent conception. Some students deny the presence of growth cycles, others offer varying numbers of cycles. Davenport⁴ is certain that there are but two cycles of growth whereas Brody⁵ divides the life span into seven stages—following Shakespeare—although only five are in the period of real growth

More recently Wetzel^o has called attention to the fact that in all previous discussions, the terms "relative growth" and "relative rate of growth" have been used as if synonymous with "relative rate of gain." He correctly points out that previous

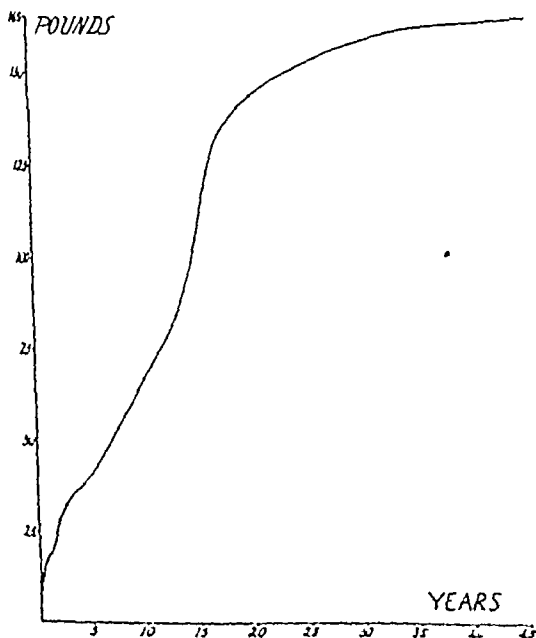


Fig. 5—Average weight curve used by Robertson to illustrate the cycles of growth and autocatalytic theory of spurts of growth (T. B. Robertson, *M.D. Pediatrics*, Vol. 1)

conceptions are based on the progress of cumulative increments of weight and the rate of gain but that the factors show no relativity. He proposes to describe true growth as a change in size per unit size, the rate of growth then would be that

expression related to a time factor. Graphs representing the equations derived by the application of his principles are

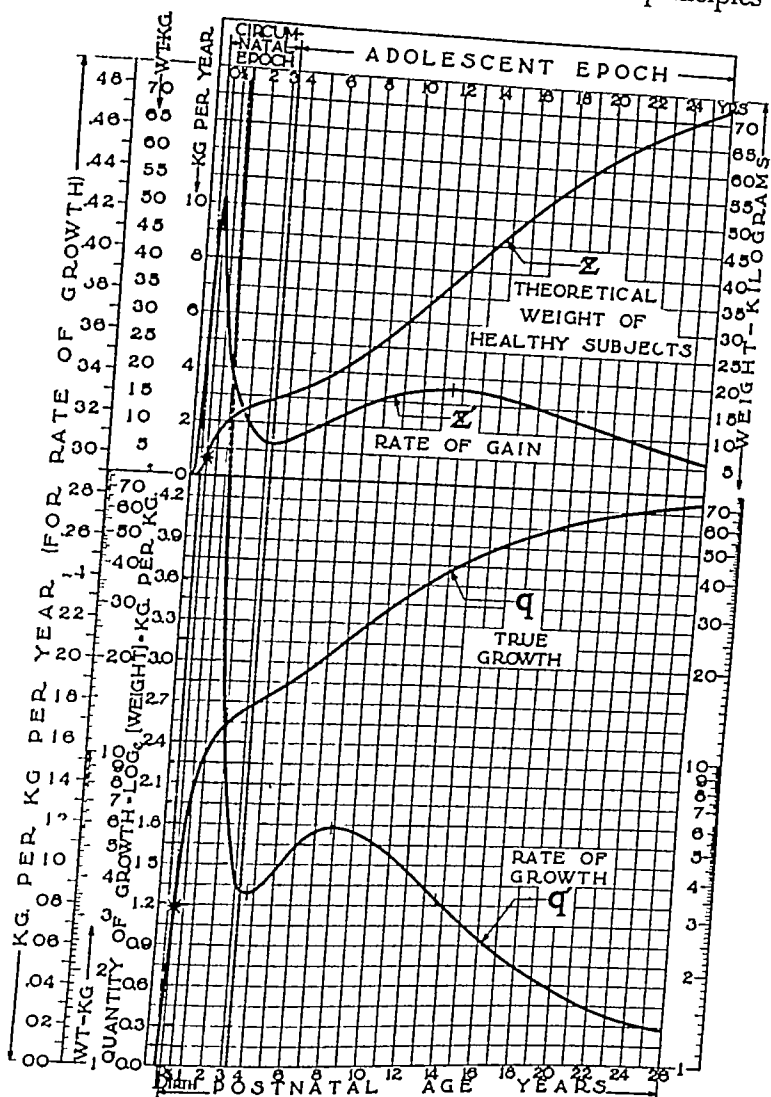


Fig 26—Curves of "True Growth" and "Rate of Growth" after Wetzell compared with curves of "Gain" and "Rate of Gain" (Wetzell, Jour of Pediatrics, April, 1934)

shown in Fig 26. His curves are presented together with the more conventional curves to illustrate the difference.

The most conspicuous difference between the weight curve

know that the human fetus at three months has a water content of 97 per cent, yet all the changes which define external form and the differentiation of organs and skeletal structures have taken place Davenport and many others insist that growth can be a qualitative as well as quantitative change provided that there be positive change toward the optimum organismic pattern

It is plainly evident that these several analyses of the method of human growth are founded on mass statistics of body weight The curves are made from mean values and therefore, demonstrate only the increase in the mean whether that be relative to age or mass or both together Unfortunately, these theories fail to help the practicing pediatrician very much for any specific child is a "rugged individualist" and never follows a summation curve in his own growth

Davenport¹⁰ demonstrated this fact clearly for growth during the adolescent epoch and any observing pediatrician or parent is aware of its validity Each epochal spurt of growth is really the mean distribution curve of numerous spurts occurring in individual children

I cannot deny that the theories of the pioneers in biomathematics are interesting nor can I assert that they are without significance but I must echo the sentiment of Ponder¹¹ who says that "until quantitative measurement has provided us with more facts of biology I prefer the former science (quantitative biology) to the latter (biomathematics) "

In addition there is another formidable objection to the practical use of mean growth or growth velocity curves E B Wilson¹² has succinctly expressed the axiom that "different aspects of the individual, or of the average, may have different types of growth curves" The work of many investigators has shown that each organ may have a variable type of growth

This leads us to the conclusion that the only way to learn how an organism grows is to study its growth

It is now generally conceded that the best way to appraise the growth of a child is to analyze a series of examinations of

that child spread over a considerable period of time. However, at any single examination, the physician may be called upon to diagnose the child's status. In the past, such a single appraisal, lacking the support of serial observations, has led too often to a grave pronouncement rather than well qualified opinion.

To enhance the virtue of such opinions, much valuable work has been done by Faber,¹³ by Gray,¹⁴ by Lucas and Pryor,¹⁵ and by Stewart¹⁶ and his associates. These workers have tried to show that children present types of body build, inherited largely, and that individuals having one type of skeletal form, grow differently than those in other types. Faber, and Stewart and his associates have enlarged the scope of this method by designating groups according to percentiles of the distribution curve of observed values or deviations from the mean.

It should be noted that such analyses of growth with reference to skeletal type facilitate the appraisal of status only in regard to quantitative measurement. Stewart alone points out the value of the use of serial analyses by such methods.

The fundamental problem however, is growth which is dynamic.

It is no doubt comforting to be able to support one's opinion that a certain short slender boy is really "normal" by reference of his observed measurements to those of other equally "normal" children in his proper skeletal group. For such support of clinical judgment the work of Stewart, and of Lucas and Pryor is invaluable. But after all, such an opinion would still be based on a greater or lesser number of anthropometric measurements.

These measurements give us information concerning the size of the skeleton plus the attached soft tissues and the mass of the body. By no such method can we derive information concerning the quality of the skeleton, the attached muscles nor any of the other organs beneath the skin. Yet all these organs and tissues are growing and maintaining some state of nutritional condition which the physician really should appraise.

To my mind no complete appraisal of a child is possible without resort to the use of descriptive terms in one's assessment of the quality of growth and of the nutritional status of certain tissues and organs. This also involves descriptions of functional performance.

It is probable that many items which now must be described may in the future be expressed in quantitative terms. In this way would the biology of man approach more closely to the galtonian conception of a science.

However, many distinguished scientists do not feel that Galton was fair when he maintained that "Until the phenomena of any branch of knowledge have been submitted to measure and number that branch cannot assume the status and dignity of science." Professor E. B. Wilson¹⁷ has recently upheld the dignity of the descriptive science and the possibility that important aspects of growth are primarily qualitative.

Only when growth is proceeding, and proceeding satisfactorily, can there be optimum function of many organs and the appearance of distinctive behavior patterns, so ably shown by Gesell¹⁸. These can only be described by word or photograph.

The appraisal of growth should include measurement of the quantity of growth of those parts which can be so measured. These measures should be few and entirely significant. The quality of the growing tissues should be described and in addition reference should be made to function. The behavior patterns express the function of the whole child and should be noted. Growth is dynamic and is best appraised by serial observation.

Since I have never been a contributor to the field which I just reviewed, my comments are to be interpreted merely as the reflections of one whose professional life is concerned with the growth of children and whose mind is fascinated by every phase of the subject. I trust that those whose work I have criticized will not have the same feelings as the author of "English Bards and Scottish Reviewers."

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CLINIC OF DR VAUGHN C GARNER

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CONTACT ECZEMA

THE complex of eczema has probably occasioned more writing and been productive of more debate than any other entity in dermatology. Yet its striking prevalence, its disabling symptomatology and its intricate background justify any attempt toward a clearer understanding of that etiologic interplay which results in an exudative inflammation of the skin, so glibly diagnosed but generally so poorly analyzed and treated. I shall attempt today to stress one of the causative factors since all the recent work in this subject has clearly indicated the trend away from the morphologic diagnosis and classification of the textbook toward a basic comprehension of the predisposing and precipitating elements in the individual case. The time has passed when any inflammatory condition of the skin of known external cause is called dermatitis, while the term "eczema" is relegated to inflammatory pictures due to unknown or hypothetical internal causation. Most present-day authorities subscribe to the identity of eczema and dermatitis since they defy clinical as well as pathological separation. As Highman¹ has aptly stated "Eczema may be of external or internal origin. If it is of external origin it could not be produced without predisposition. If it arises internally it could not be produced without a precipitating external cause." It is immaterial which term is used if one appreciates that both are inseparably bound together by ties of interlocking predisposition and indistinguishable clinical manifestations. Time does not permit exploration of the fascinating internal background of eczema, embracing as it does hereditary,

allergic, metabolic and neurogenous factors so clearly delineated by Stokes² and others. Much of this phase of the subject is still in an experimental stage of investigation and attended by uncertainties and argumentative speculation. Unfortunately the ideas of "imperfect elimination and faulty metabolism" are still perpetuated in the literature and it may be said without contradiction that comparatively little progress was made in the understanding of eczema as long as investigators sought the cause in altered blood chemistry or were content to call an eczema "gouty" simply because it was confined to the feet. The discovery that many eczematoid pictures were in reality examples of ringworm or pyogenic infection stimulated interest in local causes of exudative reaction and the past fifteen years have witnessed the gradual ascendancy of the instrumentality of contact factors in the production of many eczemas. There still remains, however, that complex allergic picture, more blessed with names than understanding, in which contact factors are of negligible importance. The table on page 321 which incorporates the combined opinions of Sulzberger,³ Stokes,⁴ Coca⁵ and other writers helps to distinguish this type of eczema from that in which external contact factors are dominant.

The list of exogenous contact allergens is legion and apparently no substance is beyond the bounds of suspicion. Practically everything touched by human hands is capable in susceptible individuals of inducing an eczematous response. Furthermore, this susceptibility may develop only after long exposure, hence a history of immunity to a possible contact factor over a period of years does not exclude its eventual incrimination. The gamut of excitants ranges from an irritating drug in a hair tonic and leather in a hat band, through the cosmetics, to the ink used in colored supplements and the dyes in footwear. Should the dermatitis induced by tobacco fumes increase we cannot even smoke in peace. Many persons are at the mercy of their environment and they react to every conceivable and even inconceivable contact. Weber⁶ in 1930 compiled a list of proved cutaneous irritants embracing

	Atopic eczema.	Contact eczema.
Synonyms.	Allergic eczema. Diabetic eczema. Eczema asthmat-hay fever complex. Neurodermatitis disseminata.	Dermatitis eczematosa. Occupational eczema. Dermatitis venenata.
Onset.	Usually before 20.	Any age—usually in adult.
Allergic family history	Positive especially for asthma, eczema, hay fever, urticaria, and vasomotor rhinitis.	Negative except by coincidence
Allergic personal history	Usually positive. May be associated or alternate with hay fever or asthma.	Usually negative.
Antecedent eczema.	Frequent history of infantile eczema.	Uncommon.
Localization.	About the eyes, mouth and neck. Flexures of elbows and knees. May generalize.	Varies widely—most commonly on exposed parts (face, hands, and forearms). Flexures rarely involved.
Predisposing back ground.	Affects any type of skin. Neurocirculatory instability usually present.	Favored by ichthyosis, seborrhea, pyogenic and mycotic infections and stasis.
Clinical appearance.	Dryness with leathery lichenification of skin.	More acute and inflammatory
Vesiculation.	Rare. May show weeping excoriations.	Vesicle formation common.
Dermatographism.	Pronounced pale Strick reaction (white dermatographism)	Average expected response.
Personality	Usually egocentric, emotionally unstable over ambitious, "poker face."	Average personality pattern.
Duration.	Many years. May disappear in the twenties or be lifelong	Usually disappears with recognition and removal of cause.
Pathogenesis.	May be mediated by water soluble antigenic excitants.	Nonantigenic excitants.
Skin test and intradermal tests.	Few to many positives. Often of questionable significance.	Usually negative and of no significance
Inactive transfer tests.	Usually positive.	Negative
Patch tests	Usually negative	Positive
Provocants.	Food and inhalants (true allergens)	(Of nonprotein chemical nature)
Prognosis.	Poor for immediate future.	Fair Best if cause can be ascertained.
Treatment	Consistent rational desensitization regime	Removal of local cause. Topical measures.

nearly 400 titles and since then there have been numerous additions to the literature. It requires the combination of encyclopedic knowledge of chemistry, particularly that of industry, with a peculiar ferreting skill in uncovering obscure causes of eczematous excitation to correctly diagnose the more puzzling expressions of eczema. Few possess such qualifications but any doctor can learn to suspect contact factors, can exhaustively inquire into occupation, habits, pastimes and

environment and can easily master the technic of patch testing. The following cases all of which have been studied within the past year illustrate the comparative ease with which many of these problems are diagnosed.

Case I.—A married woman of twenty-eight had had a recurrent eczema of the eyelids for several months. She was under excessive nervous strain and had overindulged in alcohol on occasions. Examination revealed erythematous lichenified plaques of dermatitis involving both upper lids. A physician had pronounced the condition neurogenous and prescribed sedatives and alkalis without relief. Questioning revealed that the condition invariably flared up after being at some social affair and might even disappear during a quiet week at home. Inquiry regarding cosmetics elicited the fact that the patient only used mascara on her evenings "out." The patch test with mascara was strongly positive and its discontinuance resulted in complete recovery from subsequent attacks.

Case II.—A boy of three had had an eczema of the legs said to be uncontrollable by his family doctor. As the mother undressed the lad for examination it was noted that she had markedly ichthyotic palms and subsequent inspection of the boy revealed a similar state of affairs. This condition had predisposed the skin to the daily irritating effect of soap and water plus winter exposure of stockingless legs. Proper protection, omission of soap and water and the use of mild creams caused speedy involution of an eczema induced by a contact allergen (soap) on an ichthyotic basis.

Case III.—A woman of thirty-four had an eczema of four months' duration limited to the abdomen, lower back and flanks. Her physician diagnosed the condition acidosis and prescribed soda. The sharp circumscription of the process pointed to a local factor and immediately suggested contact irritation from an elastic girdle worn for reducing purposes. Removal of the offending cause resulted in recovery within a week's time.

Case IV.—An obese woman of forty presented an acute eczema of both axillae. Her doctor said it was from acid sweat but a new green dress seemed much more logical. The patch test to this material was strongly positive. Recovery under wet dressings was prompt but a month later there was a recurrence, this time from a brown dress which had previously been worn with impunity illustrating how cutaneous sensitivities may change after an initial dermatitic explosion.

Case V.—A young man presented a bilateral linear encircling eczema of both wrists. Seeking for local causes a new wrist watch with leather strap came under suspicion and inquiry revealed that it had been transferred to the other wrist after the original site of involvement had become painful.

Case VI.—A man of forty-two who had had a Grade II seborrheic dermatitis of the scalp for several years developed moist eczematous patches over

both retroaural folds. A competent dermatologist interpreted it as an extension of the seborrheic process ignoring the fact, which only inquiry revealed, that it had appeared shortly after wearing new glasses containing nickel. The spectacles applied to the skin as a patch test gave a positive reaction and when the glasses were replaced by the shell variety the eczema abated despite the fact that no treatment of the scalp was accepted.

CASE VII.—A frail woman of forty six had had a persistent eczematous eruption, of several months' duration over both buttocks and posterior thighs. A complete allergic work up by the intradermic method had unearthed six strikingly positive reactions to foods and her doctor had insisted on an exclusion diet without noticeable change in the skin picture. Persistent questioning along contact lines finally elicited the fact that the patient treated the toilet seat with lysol two or three times weekly. Omission of this practice and a few simple local measures resulted in complete recovery even on a diet containing foods producing positive skin reactions.

These cases illustrate that inquiry is essential to the lead that uncovers the etiologic background of contact eczema. Few patients volunteer the information that points to the precipitating cause. While the history may be so clear cut that the offending substance is easily discovered, it may take weeks of observation and patch testing to accomplish it. Too many physicians rest the case on a diagnosis of "eczema" and spend futile and valuable time in seeking some as yet undiscovered panacea for its cure. I am not willing to believe that the average doctor's intelligence is measured by the absurd explanations of eczema offered by the profession and subsequently quoted by the patient. The "acid condition" myth, the indiscriminate and unjustifiable use of alkalis, the widespread use of proprietaries are all indices of the failure to grasp the basic essentials of the eczema problem.

The patch test is as indispensable in the investigation of a suspected contact eczema as is a blood count in the interpretation of anemia. Fortunately the technic is sufficiently simple to justify its more general use. The substance under investigation is placed on the unabraded skin, covered with a 1 inch square of tracing paper or cellophane and either strips or a larger square of adhesive placed on top to completely exclude air. Liquid preparations to be tested are incorporated in gauze. The reactions are read in twenty four, forty eight and

seventy-two hours In positive cases a small patch of dermatitis (erythema, papules, vesicles) will appear at the site of contact with the suspected irritant. It is important to apply the test as near to the eczematous site as possible since only adjacent areas of the skin may be sensitized In testing cases of facial eczema, use the V of the neck Sulzberger has shown that the skin of the scalp, face, hands and forearms are much more hypersensitive than the remainder of the body and as is well known most cases of contact eczema occur in that distribution

Unfortunately the eczema problem is not as simple as the quoted cases would indicate Mycotic, certain pyogen and some parasitic infections give rise to eczematous response in the skin as do the ingestion of certain drugs and the secondary toxic manifestations from initial sites of ringworm Furthermore, as Glaze⁷ has pointed out certain unrelated dermatoses may show eczematization in potentially eczematic patients so that critical exclusion must precede an acceptance of eczema from the clinical standpoint When the latter diagnosis has been reached with reasonable certainty, it is essential to estimate what part contact factors may play in it and then initiate a thoroughly planned course of attack from this angle When patch testing is approached with as much enthusiasm as the frequently valueless study of blood and urine, we shall be infinitely nearer the solution of the problem of contact eczema than we are at present

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ECZEMA IN INFANCY AND CHILDHOOD

WHENEVER the medical profession is at a loss for the true etiology of a pathological condition we find a wild profusion of theoretical causes and cures for that condition. So it has been with eczema. Years ago one could crudely define eczema as an inflammatory condition of the skin with manifestations varying from dry scales to weeping vesiculated areas, but always associated with itching. That was a good broad definition and it covered a multitude of conditions. As the years

Some would be improved by reduction of carbohydrate in the diet

In breast fed infants, in which group eczema is seen almost as frequently as in the artificially fed, the condition can sometimes be treated by altering the mother's diet but in many cases we are compelled to take the child off the breast

Few cases of infant or childhood eczema show permanent results from any form of local treatment. Most cases improve decidedly, but temporarily, when given a laxative and put on minimal diet or actually starved, as occurs in the early stages of acute infections. Many cases recover spontaneously at eighteen months to two years of age. Many cases show onset of eczema after an acute attack of enteritis.

Studying this list of facts it seems quite obvious that we are dealing with something which is definitely more than a purely local condition. There must be a fundamental peculiarity of the individual which makes his skin subject to such outbreaks. Also it seems obvious that the peculiarity is frequently, but not always, linked to the alimentary canal.

Czemy gave this peculiarity the name "exudative diathesis" and felt that cow's milk fat was particularly intolerable to these cases. Other authors have laid the blame on carbohydrates. Aschenheim (quoted by Moro in Feer's Pediatrics) felt that there was a low limit to assimilation of carbohydrates and a tendency to alimentary glycosuria.

Freund and Menschikoff (also quoted by Moro in Feer's Pediatrics) showed an increased and abnormal tendency to water and chlorine retention followed by an excessively rapid excretion when there was reduction of chlorine in the diet.

More recently A. E. Hansen¹ writes that in many cases of childhood eczema there is a low level of unsaturated fatty acids in the serum and compared these cases to the experimental fat deficiency disease of rats as described by G. O. Burr and H. M. Evans². Hansen found that many of these

¹ Proceedings of Society of Experimental Biology and Medicine, vol 30, June, 1933, pp 1198-1199

² Proceedings of Society of Experimental Biology and Medicine, vol 25, October, 1927, pp 41-48

cases could be relieved of symptoms by adding to the diet an oil high in unsaturated fatty acids. This article is particularly interesting in view of the earlier diets where fat was excluded empirically. Doubtless more will be published on this work during the current year.

In applying these facts to treatment it is at once evident that we must not limit ourselves to local applications. These should be used only to alleviate distressing symptoms while the main treatment strikes at the underlying condition. In both respects unfortunately, we are often incompletely successful.

The second important feature of treating childhood eczema is to remember that while it is a distressing disease and the symptoms require treatment, it is most important to maintain the general health of the child and to guard against the deficiency diseases, faulty bone formation and maintain adequate growth.

Bearing these two important features in mind the third step is a thorough history. Here one should dig back into the family history for the allergic diseases, mentioning them by name, rose cold, hay fever, asthma, eczema, hives, migraine, food rashes or upsets, drug idiosyncrasies. And here let me emphasize that it is not safe to trust a negative allergic history. Not infrequently a parent will repeatedly deny any such history only to admit or discover, perhaps a year later that there was a definite allergic condition somewhere in the family, perhaps in her-self or himself as the case may be.

The history should include the course of the pregnancy, then the feeding history—how long on the breast, any difficulty with the child while breast fed, frequently the mother will have noticed that certain articles in her diet would cause an upset in the child. Then the date on which the skin condition was first noticed, its location at that time and how it spread and what variations it showed. Next the dates of the various changes in diet and environment (such as soaps, woolen clothing etc.) and how they affected the condition, if at all. Changes in the skin condition during the various

seasons Changes during dentition Eczema is frequently more severe during the teething period Existence of nasal mucus or postnasal congestion of noninfectious type, frequent colds, constipation of the spastic type These conditions are frequently associated

In physical examination note first the general condition of the child—heart, lungs, bony framework, mucous membranes, lymphatic tissues and nodes Abdominal distention, etc Then check on the skin condition Rule out the parasitic diseases—dermatophytes, etc Note degree of superimposed infection Evidence of scratching, urticaria, ichthyosis, location of lesions, worse or better under clothing

Following this must come a discussion with the parents They should be told exactly what they and you are up against The probability of a long drawn out struggle, with some improvement, frequent exacerbations and disappointments, the necessity of patience, careful observation and prevention of infection and injury by scratching The probability in most cases is that in time there will be a readjustment of the individual and that as a child grows older there will be an improvement often not possible in the earlier stages

If all of this is explained at the start of treatment it will save much dissatisfaction and discouragement

While in many cases the history will reveal certain offending proteins I feel that in all resistant cases the cutaneous tests for sensitivity to foreign proteins should certainly be tried I also feel that these tests should not be limited to probable offenders but should include all proteins in the child's diet and environment and also all the proteins apt to be contacted in the near future I am quite aware that such tests are often disappointing, that they frequently give few reactions which are not sufficient to clear up the condition, or that they give so many reactions that it is impossible to eliminate all from the diet

Also, these children are liable to sudden changes in their sensitivity, especially following an acute enteritis Even so it is a help to know definitely which subjects are most to be

suspected and frequently a brilliant result may be obtained. Often in young children the skin does not react as markedly as does the alimentary canal and if the history tells of an offending food to which the skin does not react I prefer to rely on the history. If, however, the skin reveals an offender which according to the history gives no obvious trouble, I prefer to rely on the skin.

I am convinced that mildly reacting substances often require a long latent period before they cause symptoms. In some cases with a definitely known protein as the offender it is possible to make the eruption appear and disappear at will. In these cases the latent period will vary from as short a time as twenty four hours to as long an interval as two weeks. The long latent period is unusual and in practice I usually allow from three to seven days. When there are many reacting substances it is wise to start treatment with a laxative preferably either castor oil or calomel and a diet limited to nonreacting foods. Then at intervals of three days add to the diet one at a time the foods showing doubtful or minor reactions. Here it should be noted that foods, in testing, rarely show a reaction comparable to that of the pollens. A reaction which would mean little in testing against pollen would be quite significant when testing against foods. Also one should remember that milk, eggs and wheat are the most common offenders and should be kept under suspicion even when they do not react to the cutaneous tests. In young infants it is difficult to entirely eliminate milk from the diet. Here some substitution becomes necessary and it is interesting to note that in mild cases evaporated or dried milks are often tolerated when whole milk is not. In these mild cases, too, a skimmed milk may be well borne. Also I have seen cases which could tolerate a Walker Gordon certified milk when they could not take pasteurized milk. However, the reverse of this may be true. Butter flour formulas may be used and a rice flour or cornstarch may be substituted for the wheat flour. The last few years have seen several valuable additions to the list of milk substitutes—hypoallergic milk—Sobee and Lemas, a

vegetable milk, being probably the most valuable, S M A, a synthetic milk without cow's milk fat, is often of value. Personally I have found the S M A and hypoallergic formulas of greatest help in young infants, the Sobee and Cemac are better tolerated at five months or older.

It must be remembered that none of these substitutes are complete foods and the vitamin balance must be watched.

Where milk is taken out of the diet calcium should be used almost steadily. Several workers have shown it to be of value in raising the threshold of skin irritability.

Also I feel it is wise to administer meat juices and scraped or finely ground meats early in life to supply the animal proteins. Needless to state proper elimination should be maintained at all times and in the exacerbations a thorough laxative with castor oil or calomel may give temporary relief.

Glandular extracts have been used by various workers but have never come into wide general use. I have personally tried thyroid and adrenal extracts on various cases. Given by mouth, I have been unable to note any appreciable results. In relieving the intense itching the opiates often fail. Veronal has been found more useful when such sedation is necessary.

In local treatment the remedy must be varied to fit the stage of the ailment and the reaction of the individual, a remedy helpful to one individual may be of no benefit to or actually distress another. Most writers are agreed that water in itself acts as an irritant and more so when combined with soap. Bland oils are preferred for cleansing purposes and, even in the milder stages, water should be used only occasionally. Clothing should be nonirritating, anything with wool in it or even a rough or fuzzy surface seems to stir up itching even though the individual may not be sensitive to that substance. In the early acute stages with marked inflammatory reaction or weeping areas, soothing lotions should be applied. Of these a saturated boric acid solution applied as moist compresses is often most successful. Calomine is a good lotion but often forms crusts. I have seen some cases do well with a weak solution of liquor carbonis detergens—1 drachm to 4 ounces.

Two per cent aqueous solution of resorcin is often effective as an antipruritic. In the most severe cases it is sometimes necessary to use facial masks and to restrain or protect all the extremities as these infants will claw themselves until covered with blood. More chronic cases can be treated with the tar derivatives—the old favorite was ung picis liq 1 drachm, pulv zinc ox 2 drachms petrolat to make 1 ounce. In recent years newer tar derivatives have come on the market which have not the objectionable staining and odorous qualities of the older preparations but are often not as effective. Where infection is superimposed I like to use either a bath of weak potassium permanganate or a mild ammoniated mercury ointment, 2 to 5 per cent sometimes combining these treatments. x Ray is extremely useful in treating the severe explosions of symptoms but we must remember that its effect is temporary in these cases. A more lasting effect is obtained when it is used on old chronic cases to bring the thickened skin back to normal. It should only be applied by someone experienced in that type of work. Ultraviolet light seems to help some cases enormously but should be given in small doses as in many cases it seems to increase the itching.

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THE VISCERAL LESIONS OF ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS

ACUTE disseminated lupus erythematosus is a syndrome of uncertain etiology, occurring chiefly in females, and characterized by the following features (1) Polymorphic cutaneous lesions, usually appearing first on the face and thence spreading to the ears, neck, extremities, trunk, mucous membranes, and genitals. These lesions may resemble a dry, scaling or crusting eczema, or polymorphic erythemas, sometimes with vesicles and bullae. Again they may occur as large purpuric areas, or hemorrhagic papules. Local edema is sometimes present. Occasionally these acute disseminated lesions follow or are ingrafted upon chronic discoid erythematous lupus. (2) A course marked by acute exacerbations and remissions. The latter may be prolonged but death occurs within five years in the vast majority of cases.¹ Exacerbations, sometimes fulminant and fatal, are prone to follow exposure to light, removal of focal infection, or intracutaneous tuberculin inoculations. (3) Marked constitutional symptoms, which may precede the appearance of the skin lesions. These include fever of a septic type, weight loss, weakness, bone and joint pains, acute attacks of abdominal pain simulating appendiceal or gallbladder disease, urinary symptoms, impairment of vision, cough, hemoptysis, headache, dyspnea and precordial pain. (4) Visceral lesions involving the kidneys, heart, lungs, spleen, liver, serous surfaces, joints, eyes, lymphatics, and gastro-intestinal tract. Anemia, leukopenia, albuminuria

cylindruria and pyuria are common. The purpose of this communication is to describe these visceral lesions and to present 5 cases illustrating their frequency and nature.

Various unproven theories concerning the etiology of the disease have been advanced. It bears a marked resemblance in many instances to certain types of erythema multiforme, and has been thought to be a variant of it. Tuberculous or streptococcic infection, sensitization to the products of these infections, or to various metabolites (urea, hematoporphyrin, tyrosin, lactic acid, lymphocytic ferments, etc.) combined with light sensitization, skin sensitization to abnormal products of primary disease of the reticulo-endothelial system—all have been invoked as possible causes. Most observers incline to the view that some type of sepsis (perhaps streptococcic) operating in a sensitized individual, perhaps with a latent tuberculous background in some instances, produces the disease. It is obviously systemic in nature, the relation of the skin lesions to the visceral changes is not clearly understood.

Osler² in 1895 reported 11 cases of what he called erythema exudativum multiforme, with polymorphic skin lesions and various visceral changes—acute nephritis (5 cases), splenomegaly, endocarditis and pericarditis, gastro-intestinal and urinary bleeding each occurred in 3 cases. It is probable that these cases were identical with, or variants of, the syndrome under consideration.

Kidney—Renal lesions are very common in acute disseminated erythematous lupus. Keith and Rowntree³ describe four cases with renal complications. Albuminuria, cylindruria and hematuria were present in all, more marked during exacerbations of skin lesions. Blood urea nitrogen and phenol-sulphonphthalein excretion were normal. One case came to necropsy, and showed, in addition to tuberculosis of the ileum, spleen and mesenteric lymph nodes, bilateral chronic glomerular nephritis. They state that the clinical picture was that of a chronic nephrosis, despite the appearance of the kidney at necropsy. Snapper⁴ has described in some detail the renal picture in 6 cases, 4 of which came to necropsy. Acute

glomerulitis and parenchymatous nephritis were found in all. Tubular autolysis, minute abscesses with numerous hemorrhagic areas, blood in the tubules with proliferation and swelling of the loops, interstitial edema and cloudy swelling of the glomerular capsule with obliteration of the glomeruli, were also described. He points out that the symptoms of the nephritis may antedate the appearance of the skin lesions, and first cause the patient to seek assistance. Kidney lesions varying from a "mild nephrosis" to severe nephritis were found in all of 9 fatal cases by Mook, Weiss, and Bromberg.⁵ Embolic glomerulonephritis, pyonephrosis, hemorrhagic nephritis and chronic interstitial nephritis have also been described. The urinary findings are apparently not indicative of anything more specific than an acute or chronic renal irritation—albuminuria, the presence of red and white blood cells, and casts of all descriptions. Azotemia has often been reported. Modern methods of studying renal function would be of interest in erythematous lupus.

Albuminuria and cylindruria were present in all of our cases, azotemia was noted in two, marked impairment of renal function judged by change in urea clearance was not noted in two cases in which this test was done. Hypertension was present in two. Definite evidence of nephritis was found in only one of three necropsies, and in this case part of the renal picture probably antedated the onset of the acute disease by a long time.

Heart and Blood Vessels—Ulcerative and vegetative lesions on all the valves, verrucous mural endocarditis, acute fibrinous and adhesive pericarditis, and acute pericarditis with effusion, atheroma of the aorta, disseminating telangiectasis, and Raynaud's disease (all of which may have been entirely coincidental) have been described in detail by various writers. Libman and Sachs⁶ have reported what they believe to be a distinct variety of verrucous endocarditis, marked by the absence of Aschoff or Bracht-Wachter bodies, negative blood cultures, anemia, a febrile course, and absence of marked cardiac symptoms. Pulmonary symptoms, evidence of glomerulo-

nephritis, and arthritis were prominent features. Erythematous or purpuric skin lesions were present in all cases, and caused them to comment on the possible relationship between their cases and the erythematous-visceral syndrome described by Osler. The usual clinical signs and symptoms of endocarditis or pericarditis are of course found. Blood cultures usually remain sterile, and gross embolic or thrombotic phenomena do not seem to be common. Fresh vegetative mitral endocarditis was present in one of our cases, no gross embolic or thrombotic visceral processes were observed, there was no evidence of pericarditis in any case.

Liver—Hemorrhagic changes in the lobules, cirrhosis, fatty degeneration, and deep jaundice with marked hepatic enlargement⁷ have been described. The principal hepatic changes noted in our cases were engorgement, cloudy swelling and fatty degeneration. Clinical jaundice was not noted.

Lungs and Pleura—Bronchopneumonia frequently terminates the disease. This and lobar pneumonia, with pleurisy and effusion, pulmonary abscesses (single or multiple), and gangrene, and acute or chronic tuberculosis of various types, are the principal pulmonary complications. Bronchopneumonia with pleural effusion was found in the three cases of our series which were examined postmortem. Clinical findings clearly indicated the presence of pleural effusions in the other two patients. Severe terminal laryngotracheitis occurred in one of these patients.

Gastro-intestinal Tract—Gastro-intestinal symptoms, especially those referred to the upper abdomen, are common, a number of patients have been subjected to unnecessary appendectomies because of symptoms simulating acute appendicitis. The picture may closely resemble that of acute cholecystitis. Acute terminal peritonitis has been described. Ulcerative ileal tuberculosis was present in Keith and Rowntree's case. Membranous colitis has recently been described.⁸ No significant gastro-intestinal symptoms or lesions occurred in our cases.

Lymphatics—Tuberculous (often caseating) or nonspe-

cific enlargement of lymph nodes may occur in almost any location. Mesenteric, retroperitoneal, and mediastinal involvement seems to be commonest.

Adenopathy was noted in all our patients, including a subacute mesenteric lymphadenitis found at necropsy in one.

Ocular—Although two of our patients had visual disturbances due to definite papilledema, we have been able to find but few references to intra-ocular complications in the literature. One of the cases of atypical endocarditis reported by Libman and Sachs had bilateral neuroretinitis. Snapper mentions "slight papillitis" in one of his cases. Semon and Wolff¹⁰ describe subretinal exudation with invasion of the choroid. Abramowicz and Dulowicz¹¹ describe small spots lighter in color than the rest of the fundus, principally in the macula but also around the disc, whose appearance resembled that of retinitis guttata. The case of Goldstein and Wexler¹² showed discrete areas of retinal atrophy and pigmentation, the distribution being perivascular, at necropsy edema of the intima of the retinal vessels was also found. Papilledema is not discussed in any detail in the literature.

Miscellaneous—Miliary tuberculosis of the spleen, hemorrhagic splenitis and "splenomegaly" (cloudy swelling or acute splenic tumor?) are described. The joints are frequently involved—hyarthrosis and pyarthrosis have been found. Pain in the joints and extremities is common. Focal or metastatic infection is probably present in most cases—teeth, sinuses and tonsils (Madden described gangrene of the tonsil) are the common foci. Subcutaneous abscesses, cellulitis, and subperiosteal abscesses—processes to be expected in a general sepsis—are described. Secondary anemia and leukopenia are very frequent. The sedimentation rate of the red cells is said by Pick to be abnormally rapid. Low et al.¹³ describe the bone marrow as showing hemorrhagic changes and a leukoblastic reaction.

Although blood cultures are usually sterile, a variety of organisms has been recovered from blood and lesions. These include the tubercle bacillus, streptococcus (for details see

and viridans), *Staphylococcus aureus*, pneumococcus, and *Bacillus alkaligenes fecalis*. Frank clinical evidence of active tuberculosis is usually lacking, but in addition to the reported positive blood cultures, frequent reports of positive guinea-pig inoculations from lymph node material are to be found.

All of our patients had enlarged spleens, and acute hemorrhagic or septic splenitis was found in all three necropsies. Focal infection (tonsils, teeth, sinuses, prostate or pelvic organs) was present in all. Joint pain, swelling or stiffness was a constant symptom. Leukopenia was present at one time or another in all our cases and secondary anemia was noted in four of the five. Blood cultures were persistently negative in all our cases.

Case I.—H. K., a white girl of seventeen, was admitted to the medical division of the University Hospital on November 5, 1934, complaining of spots on the legs and pain in the left side of the abdomen. During the preceding year she had had vague extremity pains, and for several months had noted a faint linear eruption on the back and chest during the menses. She had lost 15 pounds in a few months. Two months before admission large purplish areas had appeared in the legs, subsequently fading but recurring with menstruation. There had been intermittent chills, sweats, and feverish sensations, blurred vision, painful cervical glandular swelling, epistaxis, cough and headache for one month. Anemia and leukopenia had been noted by her physician, and the spleen was thought to have been palpable. Within the week preceding admission there had been two attacks of sharp left hypochondriac pain and tenderness, with painful swelling around the eyes. There had been high fever for four days.

Examination showed fever (104° F), tachycardia, hypertension (152/100), axillary and cervical adenopathy, petechial lesions over the lower sternum and arms, and involuting brownish-red areas in the legs, with some scarring, soon after admission (following exposure to bright light in a sun parlor) an erythematous facial eruption appeared, the spleen and liver were vaguely palpable, there was bilateral papilledema (5D on right—4D on left) with spread of the edema into the retina, hemorrhages and venous engorgement. There was a small pleural effusion on both sides. There was a moderate anemia (hemoglobin 54 to 69 per cent, red blood cells 3,400,000 to 3,900,000), leukopenia (white blood corpuscles 5800 to 6700, with 6 to 8 per cent eosinophils), and a reduction of blood platelets to 145,000. The urine contained albumin in abundance, blood cells, and a variety of casts. Urea clearance was low normal (70 per cent of average normal function). Blood cultures remained sterile. A transient friction rub was heard over the splenic area a few days after admission. The fever gradually subsided and the skin lesions partially disappeared, but her condition did not change materially otherwise. The appearance of the eyegrounds remained the same. She was discharged December 4th.

She was readmitted to the hospital on January 31 1935. For two weeks she had had pain in both hypochondriac regions, pain and swelling in various joints, sore throat and occasional epistaxis. There had also been irregular fever, and further weight loss of 20 pounds. No fresh skin lesions had appeared. There was a fluid collection in the left pleural sac, and a long, rough apical systolic cardiac murmur had appeared. Axillary, inguinal and cervical adenopathy was present. The optic disk still showed choking, though of somewhat less degree. Blood pressure was still elevated (150/94) and the urine still contained abundant albumin and some numbers of red and white blood cells, although a very few casts were present. Blood culture was again sterile. The anemia had increased markedly, hemoglobin 52 to 28 per cent, red blood corpuscles, 2,300,000 to 1,700,000 and the leukocytes averaged 4500.

She complained much of sore throat, quite hoarse and dyspneic and attempted to cough up and expectorate mucus, with little success. On direct examination the larynx and trachea were found acutely inflamed with a coating of tough, yellowish mucus, which extended up over the epiglottis. All therapeutic measures, including several small blood transfusions, were fruitless. She became progressively weaker and more dyspneic and died on February 13 1935. Autopsy was not permitted.

Summary—Purpuric and erythematous skin manifestations of acute disseminated lupus erythematosus in a white female of seventeen, with a fatal termination after about five months. Complications included splenic enlargement (and peri splenitis?), pleural effusion, bilateral papilledema and retinal hemorrhages, arthralgias, hypertension, and severe terminal laryngotracheitis. There was albuminuria, pyuria and hematuria, but no marked impairment of renal function. The late appearance of a systolic cardiac murmur may have indicated an active endocarditis, although there was at the time a severe anemia. Leukopenia was present during most of the course of the disease. Blood cultures remained sterile.

puffy, and an erythematous rash appeared on her cheeks and nose, which soon spread to the ears, forehead, chin, and upper arms. She felt feverish and weak. The joint pains disappeared gradually, but the eruption persisted. She had lost 20 pounds in the year prior to admission. On the day before the facial eruption appeared her family physician had cauterized her cervix for profuse leukorrhea which had been present ever since the birth of her first child. Several members of her mother's family were said to have had Bright's disease, and the patient's father and one sister were diabetic.

Examination showed moderate fever (100° F) and tachycardia. There were several small ulcers at the mucocutaneous border of the lips and marked gingivitis. Bilateral cervical and inguinal adenopathy was present. A large patch of bright red, confluent maculopapular lesions was present across the bridge of the nose and on both cheeks. Somewhat similar, but more punctate and scaling lesions were found on the chin, lateral aspects of the upper arms, and legs. The uterus was moderately enlarged, the cervix was eroded and inflamed, and a profuse yellowish leukorrhea was present. The nasal borders of the optic disks were slightly blurred, and the fundi hyperemic. Blood count showed hemoglobin 82 per cent, red blood corpuscles 4,000,000, and white blood corpuscles 5000, with a normal differential count. Blood urea nitrogen was 12 mg per cent. Phenolsulphonphthalein excretion after intramuscular injection was 43 per cent in two hours. Wassermann was negative. Blood cultures remained sterile. Urea clearance was 89 per cent of average normal function, the renal concentrating power was slightly reduced. Albuminuria and pyuria were due in part to the contaminating leukorrhea. The leukocyte count varied between 5100 and 4100. The hemoglobin dropped to 75 per cent. On April 28th, a transient dry pleurisy appeared on the left side. The fever gradually subsided and the skin lesions cleared up and the patient was discharged improved on May 19th.

She was readmitted January 23, 1935. The left pleural pain and joint symptoms had recurred soon after discharge, and had been present intermittently ever since, forcing her to bed for a week in October, 1934. There had been some visual disturbance also and for two months she had been quite dyspneic. She had lost more weight and her hair had been falling out. The facial eruption had recurred intermittently, usually coinciding with exacerbation of the other symptoms. At this time there was very little evidence of the skin eruption, except for a reddish, discoid lesion on the chin. Her blood pressure was 140/108. Adenopathy had appeared in the right axilla. There were signs of bilateral pleural effusion, fever (100° to 104° F) and tachycardia. The spleen and liver were enlarged. Thoracentesis yielded straw-colored or blood-tinged fluid on several occasions, the cytology was not noteworthy, cultures were negative, and inoculation of guinea-pigs produced no evidence of tuberculosis. An acute sore throat developed on January 29th, continuing for four days. There was occasional slight hemoptysis (no tubercle bacilli were found in the sputum). Choking of 2 to 3 diopters was present in both optic disks. The facial eruption recurred early in February, together with erythematous lesions on the abdomen and chest. The leukocyte count varied from 8500 to 5100. She complained much of headache and joint pains, and several thoracenteses were necessary to relieve her dyspnea. Her fever gradu-

ally subsided, she became fairly comfortable and was discharged at her own request on March 8 1935

She was admitted for the third time on March 22nd again with fever headache dyspnea, and chest pain, and presenting vesicular and crusted lesions on the face At the time of this writing she is still in the ward, gradually growing worse with an irregular septic type of fever bilateral pleural effusion evidence of acute pericarditis a progressive anemia, slight leukopenia (white blood corpuscles 5100) a reduced serum protein and persistence of bilateral papill edema The blood urea nitrogen remains normal urea clearance is still 67 per cent of average normal function and the phenolsulphonphthalein output is 25 per cent in two hours The urine still contains varying amounts of albumin a few casts and many pus cells The blood pressure averages about 140/100

Summary—Acute disseminated lupus erythematosus in a twenty year-old white female, of about fourteen months' duration, its course has been marked by several exacerbations, a septic fever, arthralgia incontinua, normal or slightly low leukocyte counts, enlargement of liver and spleen, pleurisy with effusion, pericarditis bilateral papilledema, and hypertension Definite evidence of nephritis has not yet been obtained, and no findings suggestive of endocarditis have appeared Various types of therapy have been of no avail

Case III.—Mrs. G D., aged twenty five was admitted to the dermatologic service of Dr. John H. Stokes at the University Hospital on March 27 1934 complaining of pain and swelling in the ankles and wrists and an eruption on the face and lower right leg Her symptoms had begun in June 1930 with an erythematous facial eruption and falling hair She received various types of therapy including injections of gold sodium thi sulphate, and by April 1931 the eruption had disappeared In June 1931 there was a recurrence ushered in by polyarticular stiffness pain and swelling with fever—the skin lesions reappeared after exposure to sunlight There was an ulcer in the roof of the mouth at this time She remained in bed for two months and the skin eruption again cleared up In January 1934 there was another exacerbation similar to that of June 1931—these symptoms had recurred intermittently together with an eruption on the right leg until the time of admission There had been some dyspnea, rough palpitation and ankle edema since December, 1933 There was a vague history of transient joint pains in girlhood

On admission she showed fever tachycardia in terms cervical adenopathy a mildly enlarged spleen, slight cardiac enlargement with a loud rumbling systolic murmur slight hardness of the right precordium and a large ulcer on the roof of the mouth There was a marked facial erythema involving the nose malar region, and a circumoral area erythema of a purpuric type on the nose and forehead the face back, neck and arms had streaks and slight lower extremities There was marked dyspnea There was anemia and mild proteinuria

globin 60 per cent, red blood corpuscles 3,100,000, white blood corpuscles 7800 to 1380), albumin, casts and excessive leukocytes were present in the urine, the blood urea nitrogen was 12 mg per cent, intravenous phenolsulphonphthalein was 70 per cent excreted in two hours, blood cultures remained sterile. Evidence of sinus and dental infection was obtained. The blood sedimentation rate was markedly increased.

Her condition remained about the same, an intermittent fever persisting, until May 17, when there was a sharp rise in temperature, prostration, and an exacerbation of joint pains and the skin lesions. On May 28th, signs of consolidation appeared in the left lower lobe. She received three blood transfusions without benefit, and died, with high terminal fever, on June 2nd.

At necropsy the following findings were noted. Exudative fibrinous mitral endocarditis and myocardial hypertrophy, bilateral patchy bronchopneumonia, with a small pleural effusion on each side, passive congestion and parenchymatous degeneration of the liver and kidneys, septic splenitis with patches of extensive hemorrhagic exudate. The renal tubular epithelium was swollen and hazy, and the vessels were dilated and engorged with blood.

Summary—A fatal case of acute disseminated lupus erythematosus in a white female of twenty-five, the course extending over about four years, with at least 3 exacerbations in that time. The skin lesions were widely scattered, and were erythematous, papular and purpuric in type. Oral ulceration was present. There were present albuminuria, anemia, and leukopenia. Renal function was probably normal. The visceral lesions included endocarditis, bronchopneumonia and pleural effusion, septic splenitis, and degenerative changes in the kidneys and liver.

Case IV—W Z, a white male of twenty-five years, was admitted to the dermatologic service of Dr. John H. Stokes at the University Hospital on September 26, 1934, complaining of an eruption on the face and hands, malaise, fever, and joint pains. In the spring of 1934, a red patch appeared on his nose, this was soon followed by a sore throat, enlarged cervical nodes, and polyarticular pain and swelling. The facial eruption spread, involving his ear, and the lesions became painful. Frequent epistaxis occurred. He lost weight and strength progressively, ran an irregular fever, and had almost constant discomfort in his throat. His hair had begun to fall out. Before admission to the ward he had received several injections of gold sodium thiosulphate in the out-patient clinic. His past history included attacks of cellulitis with abscess formation on the left foot and right knee seven years previously, and vague joint symptoms (pain and stiffness) in childhood.

Examination on admission showed moderate fever (101° F) and tachycardia, some injection of the pharynx, and enlargement of the cervical, supraclavicular, axillary, inguinal and right epitrochlear lymphnodes. Most of the

joints were tender and painful on motion. Blood pressure was 100/60. The spleen was palpable. Red to purplish erythematous scaling confluent plaques were distributed over the face, ears, neck, right suprasternal notch, dorsal surfaces of the hands and extensor surface of the left wrist. The face eyelids and lips were edematous. There were small reddish macules on the finger pads. The cranial hair was thinned. The leukocyte count varied from 10 000 to 2800, with a normal differential count there was no anemia. Marked albuminuria was constantly present, with occasional showers of casts. Blood urea nitrogen was 12 mg per cent on October 2nd but had risen to 24 mg. on October 17th. Four blood cultures were sterile. Various types of therapy, including quinine, calcium intramuscular injections of whole blood several blood transfusions, and pentnucleotide did not influence the rapid progress of the disease. There was terminal leukopenia (without selective neutropenia) and hyperpyrexia death occurred October 18 1934.

The principal findings at necropsy included bilateral bronchopneumonia with small bilateral pleural effusion splenomegaly with hemorrhagic splenitis, and fatty degeneration of the liver. The heart and kidneys showed no significant changes.

Summary—A fatal case of acute disseminated lupus erythematosus in a white male of twenty five, of about five months' duration, with minor remissions. In addition to the extensive cutaneous lesions, the chief clinical features were arthralgia, adenopathy, splenomegaly, fever, weight loss, leukopenia, albuminuria and azotemia. Necropsy showed bronchopneumonia and pleural effusion—no evidence of kidney or heart damage was found. Repeated blood cultures were sterile.

Case V.—(Reported through the courtesy of Dr. Samuel Bradbury V. C. Lamer and F. D. Lynch.)

Mrs. C. D., white, aged forty two, was admitted to the service of Dr. Samuel Bradbury at the Germantown Hospital January 18 1935 complaining of bruise spots, sore throats, and an itching skin eruption. For the past three years she had lived easily with occasional nausea frequent profuse nosebleeds, and a tendency to bruise easily. Her symptoms had been markedly increased in the past 12 months and she had vomited blood on several occasions. Late in December 1934 an itching eruption appeared on the left palm and wrist. This quickly spread over the entire body. Past medical history was unimportant.

Examination showed slight fever and numerous purpuric spots scattered over the entire body together with a widespread vesiculopapular eruption, many of which lesions were secondarily infected. Both palms were covered with small vesicular lesions. A slightly indurated erythematous eruption covered the cheeks eyelids, and ears and extended down over the upper chest. The condition was associated with purpuric lesions. Blood pressure was 165/95. A white blood count was 12 000 with 10% polymorphonuclears. The rest of the blood count was normal. Examination of the eyes and ears showed no

abnormalities There was marked secondary anemia (hemoglobin 27 to 30 per cent, red blood corpuscles 2,070,000 to 3,050,000) White blood cells varied from 11,400 to 11,800 The differential count was not remarkable except for a slight eosinophilia Platelets numbered 131,200 The urine contained a cloud of albumin Blood urea nitrogen was 66 mg per cent on admission, and increased progressively to 74 mg per cent and 108 mg per cent

A blood transfusion was given soon after admission without apparent benefit Her condition grew steadily worse Fresh purpuric lesions appeared and vomiting became very troublesome She became drowsy, then comatose and died on January 26th

Necropsy findings included slight cardiac hypertrophy with atheromatous aortitis, bilateral lower lobe pneumonia, and an enlarged spleen engorged with blood The kidneys were small and firm with adherent capsules The renal cortices were markedly thinned and the cut surfaces had a dull glistening sheen suggestive of amyloid disease, although the iodine test was negative The mesenteric lymph nodes were slightly enlarged and showed subacute inflammatory changes Microscopic examination of sections from the kidneys showed chronic arteriolar nephrosclerosis and chronic pyelonephritis

Summary—A fatal case of acute disseminated lupus erythematosus in a white female of forty-two with acute symptoms of about one month's duration Purpuric manifestations were marked and the history suggested a possible preceding purpuric state of about three years' duration There was marked anemia and azotemia At necropsy terminal pneumonia, splenic engorgement, and chronic nephritis were the chief findings

A review of these cases supports the conception that the disseminated skin lesions are not the principal feature of the disease, but rather the cutaneous expression of a generalized systemic disorder, whether it be a sepsis, a "toxemia," or what not The visceral lesions probably persist or progress during phases of cutaneous remission Several of the clinical aspects bear a striking resemblance to subacute bacterial endocarditis It seems probable that the syndrome described by Osler as erythema exudativum multiforme, and the cases of atypical endocarditis with facial erythema described by Libman and Sachs are either variants of, or identical with, disseminated lupus erythematosus As has been previously pointed out, it is unfortunate that the term "lupus" should have come to be associated with this syndrome, in view of the fact that a tuberculous background or etiology has not been proven and that

the occurrence of marked papilledema as an ocular complication, which has been described but rarely in the literature. The importance of avoiding exposure to light, and of extreme caution in removing focal infection in these patients is again mentioned.

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